DOES NOT CIRCULATE

VOL. 48 OCTOBER, 1954 No. 4

AMERICAN HEART JOURNAL

AN INTERNATIONAL PUBLICATION FOR
THE STUDY OF THE CIRCULATION

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Vol. 48, No. 4, October, 1954, American Heart Journal is published monthly, by The C. V. Mosby Company, 3207 Washington Avenue, St. Louis 3, Missouri, entered as second class matter January 23, 1917 at the Post Office at St. Louis, Missouri, under the Act of March 3, 1879. Additional entry authorized at Jefferson City, Missouri. Subscription Price: United States, and its Possessions, per year $12.00; Canada $13.00; Foreign $13.50. Printed in the U. S. A.

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American Heart Journal

VOL. 48 | OCTOBER, 1954 | No. 4

Original Communications

CALCIFIC AORTIC STENOSIS: STUDY OF SERUM CHOLESTEROL

WITH OBSERVATIONS ON CALCIFIC AORTIC STENOSIS IN FAMILIAL XANTHOMATOSIS AND HYPERCHOLESTEREMIA

ERNST P. BOAS, M.D., SAMUEL K. ELSTER, M.D., AND DAVID ADLERSBERG, M.D.

NEW YORK, N. Y.

ALTHOUGH 50 years have passed since Mönckeberg[1] described the microscopic structure of the lesion of calcific aortic stenosis and concluded that the disease process is closely allied to the senile form of arteriosclerosis, no agreement has been reached as to the etiology of this form of valvular heart disease. Attempts to differentiate a rheumatic from an arteriosclerotic process have relied largely on anatomicopathologic studies.

It has long been our impression that many patients with calcific aortic stenosis manifest the clinical pattern of persons with certain types of atherosclerotic heart disease. Although about one-fourth of them have experienced frank rheumatic infection in childhood or youth, the progress of the valvular lesion is not associated with manifest further rheumatic activity. Calcific aortic stenosis is most common after age 50 and is often accompanied by the anginal syndrome.[2] Heart failure is relatively uncommon and when it occurs it comes late in the course of the disease. Kumpe and Bean[3] made the interesting observation that 35 per cent of their patients with advanced aortic stenosis gave a family history of hypertension, coronary artery disease or hemiplegia, suggesting a relationship between aortic stenosis and atherosclerosis.

If atherosclerosis plays a significant role in the evolution of the lesion of calcific aortic stenosis, one would expect to encounter a disturbed lipid metabolism, manifested by an elevation of serum cholesterol, with about the same frequency as in patients with coronary artery disease. We have, therefore, studied the serum cholesterol levels in patients with calcific aortic stenosis.

Three of our patients had familial xanthomatosis and one had familial hypercholesteremia. Their case histories will be presented briefly.

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Presented at the Scientific Sessions of the 26th Annual Meeting of the American Heart Association, Atlantic City, N. J., April 11, 1953.

This study was supported (in part) by research grant H-564 from the Division of Research Grants and Fellowships of the National Institutes of Health, United States Public Health Service.

Received for publication Sept. 18, 1953.

PLAN OF STUDY

We examined eighty-six patients with aortic stenosis of whom forty-three were men and forty-three women, and sixty-seven patients with chronic rheumatic valvular disease who did not have aortic stenosis. Of the latter, twenty-two were men and forty-five women. Most of the patients were derived from the practice of one of us (E.P.B.), a few from the wards of Mount Sinai Hospital. Some 90 per cent of all the patients were Jews and persons of approximately the same socioeconomic status. They sought medical advice because of symptoms of heart disease, not for any specific disease condition. The patients with aortic stenosis and those with chronic rheumatic valvular disease were derived from the same population groups.

Three-fourths both of the men and of the women with aortic stenosis were over age 50, the average age of the men was 58 ± 10.6, of the women 57.6 ± 11.5 years. Twenty-two of the men and eighteen of the women had "pure" aortic stenosis; in twenty of the men and sixteen of the women there was an associated aortic insufficiency; and in one man and in nine women there were multivalvular lesions. In the absence of necropsies and special roentgen studies, we are unable to state how many of these patients actually had calcific aortic stenosis, but it is probably safe to assume that most of those with solitary aortic lesions exhibited calcification.

The controls with chronic rheumatic valvular disease were younger than those with aortic stenosis: the average age of the men was 47.3 ± 18.2, of the women 46.7 ± 13 years. Forty-four had mitral stenosis, three mitral insufficiency, ten aortic insufficiency, and ten had multivalvular lesions.

Cholesterol determinations were made by the Sperry-Schoenheimer method. All values are expressed as milligrams per 100 ml. serum.

CRITERIA FOR THE DIAGNOSIS OF AORTIC STENOSIS

We employed the following criteria for the diagnosis of aortic stenosis:

1. A systolic thrill accompanied by a harsh systolic murmur at the aortic area.
2. A Grade 4 to 6 harsh systolic murmur at the aortic area.
3. A Grade 4 to 6 systolic murmur audible all over the precordium, even if loudest at the apex.

An accompanying diastolic murmur or a history of syncope or of angina pectoris fortifies the diagnosis.

We have had the opportunity of observing the evolution of the classical physical signs of aortic stenosis in many patients whom we have had under observation for 10 or more years and on the basis of these studies are confident that the above criteria will rarely lead to an incorrect diagnosis.[4]

Evidence is accumulating that idiopathic hypercholesteremia reflects an error of lipid metabolism, probably on a hereditary basis.[5] On the basis of some studies[6] the statement is warranted that the patients who manifested hypercholesteremia had had this disorder for many years preceding the time of examination and onset of symptoms.

RESULTS

Table I presents the over-all picture. Standard deviations are not included in this table because they would not be very meaningful in view of the small size of the sample in each age group.

Serum cholesterol levels have been shown to vary with age[7-10]; consequently, estimates of hypercholesteremia must be based on age specific standards. Keys and his colleagues[7] have published age specific standards, based on large samples, for healthy middle class men of North European extraction. No comparable standards exist for women. Keys and associates,[7] however, have published values which show that between the ages of 17 and 30 years the mean serum cholesterol levels for men and women do not differ. There is contradictory evidence concerning the relation of the mean serum cholesterol levels for older men and women. Two studies,[8,9] based on relatively small samples, indicate that the mean serum cholesterol level for women may be higher than that for men in the older age groups, but a third study[10] did not find such a difference.

TABLE I. MEAN SERUM CHOLESTEROL IN MILLIGRAM PER 100 ML. OF PATIENTS WITH AORTIC STENOSIS AND PATIENTS WITH RHEUMATIC VALVULAR DISEASE

AGE RANGE	AORTIC STENOSIS				RHEUMATIC VALVULAR DISEASE			
	FEMALES		MALES		FEMALES		MALES	
	NO. OF CASES	MEAN SERUM CHOLESTEROL	NO. OF CASES	MEAN SERUM CHOLESTEROL	NO. OF CASES	MEAN SERUM CHOLESTEROL	NO. OF CASES	MEAN SERUM CHOLESTEROL
17	0	—	0	—	1	261.0	0	—
18–22	0	—	0	—	0	—	4	236.8
23–27	0	—	0	—	2	233.5	0	—
28–32	0	—	0	—	3	183.7	2	217.0
33–37	4	290.0	1	257.0	7	208.6	2	220.0
38–42	0	—	4	214.5	6	243.5	1	177.0
43–47	5	299.0	4	275.5	2	203.0	2	247.5
48–52	3	339.3	4	231.0	5	237.8	1	213.0
53–57	8	294.0	5	238.8	7	275.4	3	256.0
58–62	8	309.0	6	293.2	7	247.6	2	198.5
63–67	6	305.2	9	271.1	4	280.8	1	223.0
68–72	5	322.8	8	223.2	0	—	2	188.0
73–77	3	243.3	2	307.5	1	241.0	1	261.0
78–82	1	315.0	0	—	0	—	1	170.0
Totals	43		43		45		22	

Fortunately, we have at our disposal serum cholesterol determinations for 257 men and 197 women made by the research division of the Sidney Hillman Health Center which can help to resolve this question. These represent part of a major study on the incidence of atherosclerosis in a union population (The Amalgamated Clothing Workers of America) and were obtained from a true random sample of the union population over age 40.[11] Table II presents these figures. All persons with clinically diagnosable atherosclerosis, hypertension, or diabetes have been excluded. We mention this specifically for to the best

of our knowledge it has not been employed in other series based on studies of hospital patients or of clinically normal persons.[7,10] In each age group, except the males for age group 40 to 42, the mean age coincided almost exactly with the midpoint of the age range. The mean age for the males in age group 40 to 42 was 40.8 years, thus almost coinciding with the midpoint of the 38 to 42 years age group.

TABLE II. TOTAL SERUM CHOLESTEROL IN MILLIGRAM PER 100 ML. OF CLINICALLY NORMAL PERSONS*

AGE RANGE	MALES			FEMALES			TOTAL		
	NO.	MEAN	S.E.M.†	NO.	MEAN	S.E.M.	NO.	MEAN	S.D.‡
33–37	0	—	—	9	215.7	5.6	9	215.7	47.8
40–42	24	227.1	7.5				56	223.2	37.7
38–42				32	220.3	5.2			
43–47	31	226.0	8.2	36	223.3	6.4	67	224.4	41.5
48–52	27	249.5	10.1	46	248.7	8.2	73	245.0	54.4
53–57	54	232.2	5.6	38	231.8	6.5	92	232.0	40.4
58–62	62	231.7	5.4	28	244.8	7.2	90	235.8	41.1
63–67	45	222.4	5.5	7	221.7	4.2	52	222.3	36.1
68–72	14	216.7	9.4	1	190.0	—	15	214.9	34.5

*Sidney Hillman Health Center data
†S.E.M. = standard error of the mean
‡S.D. = standard deviation

There is no significant difference between the male and female values at any age level. The greatest numerical difference occurs at the age interval 58 to 62. The probability that this is due to chance is about 0.14. Because the data show no difference between the cholesterol levels of the males and females, the data have been combined in the last column of Table II. These figures have been used to compute the serum cholesterol level which only 5 per cent of a sample of healthy individuals would be expected to exceed (Table III).

TABLE III. MEAN SERUM CHOLESTEROL LEVELS IN MILLIGRAM PER 100 ML. AT VARIOUS AGES*

AGE RANGE	KEYS			HILLMAN CENTER			UPPER 5% LEVEL	
	NO.	MEAN SERUM CHOLESTEROL	S.D.	NO.	MEAN SERUM CHOLESTEROL	S.D.	KEYS	HILLMAN CENTER
33–37	56	200.4	±43.1	9	215.7	±47.8	272	294
38–42	62	219.4	±38.6	56	223.2	±37.7	284	285
43–47	98	235.5	±37.2	67	224.4	±41.5	297	293
48–52	98	248.3	±44.8	73	245.0	±54.4	323	334
53–57	90	255.7	±45.6	92	232.0	±40.4	332	298
58–62	69	253.3	±33.6	90	235.8	±41.1	309	303
63–67	45	236.7	±34.3	52	222.3	±36.1	294	282
68–72	42	224.6	±41.5	15	214.9	±34.5	294	272

*The data of Keys are compared with those obtained at the Hillman Center.

Table III presents the mean serum cholesterol levels, their standard deviations, and the upper 5 per cent levels at various ages as determined from the Hillman Health Center data. For comparison, we have included the values published by Keys and his colleagues.[7]

There appears to be a systematic difference between the two sets of data; Keys' standards are lower than the Hillman standards for the two youngest age groups and higher for the remaining age groups. The means for age groups 53 to 57 and 58 to 63 are different at the 1 per cent level of significance while those for the age group 63 to 67 differ at the 5 per cent level. None of the other differences approach statistical significance.

The lower mean values obtained for the older age groups in the Hillman sample have many possible explanations, among them being the ethnic and socioeconomic differences between the two samples. It is highly probable that the Hillman Center data are better standards for our study because they are based on a population which is very similar to that of our study. As a precaution, however, we have decided to analyze our data using both sets of standards.

Using the upper 5 per cent levels shown in Table III we have classified the cholesterol values of all patients. The results are shown in Table IV. Regardless of which set of values is used it appears that the females with aortic stenosis show a significantly increased frequency of high cholesterol levels as compared

TABLE IV. NUMBER OF PATIENTS WITH HYPERCHOLESTEREMIA*

AGE RANGE	AORTIC STENOSIS				RHEUMATIC VALVULAR DISEASE			
	MALE		FEMALE		MALE		FEMALE	
	STANDARD USED				STANDARD USED			
	KEYS	HILLMAN CENTER	KEYS	HILLMAN CENTER	KEYS	HILLMAN CENTER	KEYS	HILLMAN CENTER
18–22	0	0	0	0	2	2	1	1
23–27	0	0	0	0	0	0	1	1
28–32	0	0	0	0	1	1	0	0
33–37	0	0	2	2	0	0	0	0
38–42	0	0	0	0	0	0	1	1
43–47	2	2	1	1	0	0	0	0
48–52	0	0	2	2	0	0	0	0
53–57	0	1	2	2	0	1	1	3
58–62	3	4	4	4	0	0	1	1
63–67	2	2	4	5	0	0	1	2
68–72	0	2	4	5	0	0	0	0
73–77	1	1	1	1	0	0	0	0
78–82	0	0	1	1	0	0	0	0
Total	8	12	21	23	3	4	6	9
% Hypercholesteremic	18.6	27.9	48.8	53.5	13.6	18.2	13.3	20.0

*Incidence of hypercholesteremia in patients with aortic stenosis and in patients with rheumatic valvular disease—based on upper 5 per cent level (see Table III, last column).

to females with rheumatic valvular disease (P approximately 0.01), while the males do not show this (P approximately 0.5). The incidence of hypercholestermia among patients with rheumatic valvular disease corresponds closely to that found in an unselected hospital population by one of us.[8]

There is no difference between the average serum cholesterol levels of patients with "pure" aortic stenosis and those with an associated aortic insufficiency or mitral valvular disease. Attempts to correlate serum cholesterol levels with a history of rheumatic fever, a long-standing murmur, hypertension or angina pectoris revealed no significant relationships.

Some of the clinical features of the patients are recorded in Table V. Hypertension is uncommon among patients with aortic stenosis. Nine of the forty-three males, and eleven of the forty-three females exhibited blood pressures above 150 mm. Hg systolic and 90 diastolic. Only three patients, one man and two women, with aortic stenosis had diabetes.

TABLE V. CLINICAL MANIFESTATIONS OF PATIENTS WITH AORTIC STENOSIS AND PATIENTS WITH RHEUMATIC VALVULAR DISEASE

CLINICAL MANIFESTATIONS	NUMBER OF CASES			
	AORTIC STENOSIS		RHEUMATIC VALVULAR DISEASE	
	MALE	FEMALE	MALE	FEMALE
Systolic thrill	22	12	0	0
Angina pectoris	21	15	0	0
History of rheumatic fever	8	12	8	19
Known murmur for 10-plus years	22	18	9	19
Aortic diastolic murmurs	21	21	9	12
Mitral stenosis	1	6	14	42
Total cases	43	43	22	45

Only one of the patients with calcific aortic stenosis had had a demonstrable myocardial infarct, and this was a woman with severe familial xanthomatosis. Fifteen had normal electrocardiograms, fifty-six exhibited the pattern of left ventricular strain, two had left bundle branch block, six right bundle branch block, one a partial atrioventricular block, and three complete atrioventricular block; two showed right-axis deviation, and one had only auricular fibrillation. There was no significant difference between the sexes.

CALCIFIC AORTIC STENOSIS IN XANTHOMATOSIS AND IN FAMILIAL HYPERCHOLESTEREMIA

Four of our cases give strong support to the view that hypercholesteremia may be a significant factor in the development of calcific aortic stenosis. Three had essential familial xanthomatosis with marked hypercholesteremia and one had familial hypercholesteremia.

CASE REPORTS

CASE 1. M. K. has been reported elsewhere together with her family history[12] but at that time we were unaware that she had aortic stenosis. She had rheumatic fever at the ages of 10 and 16. Tendon xanthomas were first noted at age 22. When she was 23 she began to experience angina pectoris on exertion. At age 29 the presence of a mitral stenosis was recognized. She had massive tendon xanthomas on the hands and in the Achilles tendons. Her serum cholesterol ranged from 420 to 707 mg. per cent, the cholesterol esters from 275 to 340 mg. per cent. During the last 8 years of her life she had increasingly severe and frequent anginal attacks. There was little change in her physical findings except that at age 37 a systolic murmur was heard at the aortic area. She died at age 37 from an anterior myocardial infarction. Autopsy showed severe coronary artery sclerosis, calcific aortic stenosis, and mitral stenosis, as well as an acute anterior myocardial infarct.

CASE 2. P. B. first seen at age 60, complaining of angina pectoris. He had no rheumatic history. He exhibited marked tendon xanthomas and had a well-defined corneal arcus. The heart was not enlarged. There was a harsh systolic murmur at the apex, and a systolic murmur of lesser intensity at the aortic area. Blood pressure was 125/80 mm. Hg. His serum cholesterol was 450 mg. per cent with esters 300 mg. per cent. The electrocardiogram showed right bundle branch block. The following year he complained of no further anginal pain. There was some enlargement of the left ventricle. There was a harsh systolic murmur at the aortic area, Grade 4, and a Grade 3 systolic murmur at the apex. There were no thrills. The electrocardiogram was unchanged. The serum cholesterol was 350 mg. per cent.

CASE 3. I. M., female, had had xanthelasmas of the eyelids since the age of 35. One sister examined at age 56 also had xanthelasmas, angina pectoris, and a serum cholesterol of 455 mg. per cent. At the age of 58, the patient had a normal-sized heart with a systolic murmur audible all over the precordium. At age 61 there was some enlargement of the left ventricle with harsh systolic murmurs at the apex and aortic area. The blood pressure was 130/85 mm. Hg. At age 65, the xanthelasmas of the eyelids were unchanged, there was no corneal arcus. There was some enlargement of the left ventricle. There was a harsh Grade 4 systolic murmur at the aortic area, and a Grade 3 systolic murmur at the apex. There was no thrill. The electrocardiogram was normal. The serum cholesterol was 305 mg. per cent, the esters 220.

CASE 4*. C. T., a male aged 20 years had first developed a swelling over the dorsum of one elbow at the age of 4. Soon many similar tumors appeared on the extensor surfaces of various joints, and yellow plaques developed behind the ears and around the eyes. The Achilles tendons became thick and nodular. At age 7, the serum cholesterol was 440 mg. per cent. Biopsy of a nodule revealed xanthomatous tissue. At age 10, there was severe dyspnea and palpitation. At age 12, a systolic murmur was heard at the aortic area. The tumors had increased in size. At age 13, dyspnea increased and the ankles became swollen. At age 15, many tumors were excised but they soon reappeared. The serum cholesterol ranged from 357 to 682 mg. per cent. At age 18, severe nocturnal paroxysmal dyspnea developed. At age 20, he exhibited typical advanced xanthoma tuberosum and tendinosum with xanthelasma. The heart was enlarged. There was a harsh systolic murmur and a systolic thrill at the aortic area. The blood pressure was 110/85 mm. Hg. The electrocardiogram gave evidence of left ventricular hypertrophy. There was severe left-sided heart failure.

A few similar cases have been reported in the literature. Poensgen[13] observed a 12-year-old boy with xanthomatosis, a large left ventricle, and aortic stenosis. No detailed physical or necropsy findings are given. Low[14] studied a girl of 11 who had had no rheumatic fever and who exhibited tendon and skin xanthomas. The heart was enlarged with a heaving impulse. There was a loud systolic murmur audible all over the precordium, loudest at the aortic area and transmitted to the neck. Cook and associates[15] reported the case of a boy

*We are indebted to Dr. David P. Barr of The New York Hospital-Cornell Medical Center, for making this case available to us.

aged 13 who had had tendon xanthomas for 7 years and symptoms of angina pectoris for 8 months. His serum cholesterol was 561 mg. per cent. At autopsy he had advanced coronary artery sclerosis with marked narrowing of the anterior descending branch. The aortic cusps were thickened and fibrous.

DISCUSSION

Karsner and Koletsky[16] among pathologists are the chief advocates of the view that calcific disease of the aortic valve is the result of rheumatic heart disease. They base their conclusions on pathologic study of 200 cases. They found macroscopic and microscopic stigmas of previous rheumatic infection in 91 hearts and microscopic evidence in all but four of 109 hearts. However, histologic lesions reflecting previous rheumatic infection are so common (Hall and Anderson[17] found them in 90 per cent of hearts free of manifest valvular disease) that this finding alone is not convincing. It is unnecessary to review the whole literature in detail for such a critical analysis is found in the monograph of Karsner and Koletsky. Most clinicians have followed the lead of Christian[18] in concluding that calcific aortic stenosis is a manifestation of rheumatic heart disease.

We shall confine ourselves to quoting a number of studies that to our minds prove that atherosclerosis is an important factor in the genesis of many cases of calcific aortic stenosis. Mönckeberg[1] described the lesion beginning as a thickening of the base of the aortic cusps on the side facing the sinuses of Valsalva. Here he found fatty changes, crystals, spotty necrosis, and calcium deposits without evidence of inflammation. The process gradually spread up the valve leaflet, with ever greater calcium deposition, but did not reach the ventricular surface of the valve. Dewitsky[19] noted hyalinization, fine fat deposits, and at a later stage fat crystals and calcification of the valve leaflet. Ribbert[20] gave an excellent description of the evolution of the atherosclerotic process of the aortic valve that eventually leads to gross deformity and stenosis. He pointed out that the end stage of the lesion is difficult to differentiate from one arising from inflammatory causes. Anitschkow[21] described atherosclerotic lesions of the heart valves and stated that these did not lead to deformation of the valves. He found that atherosclerosis develops with greater intensity in valvular scar tissues caused by a previous endocarditis. Sohval and Gross[22] studied eighteen hearts with calcific aortic stenosis in which there was no microscopic evidence of a previous rheumatic infection and compared the lesions with those in thirty-two hearts showing evidence of extinct rheumatic infection. They found the earliest changes in the fibrosa layer. Sclerotic and hyaline transformation of the collagen within this layer was followed by lipoid changes with deposition of globular, amorphous, and crystalline calcific material. They concluded that the Mönckeberg lesion was a purely degenerative process. They suggested that the frequent association of this lesion with inflammatory disease resulted from the mechanical strain caused by the imperfect valve, and that in susceptible persons this favored deposition of lipoid and lime in the fibrosa layer eventually giving the picture of Mönckeberg sclerosis. Lesnick and Schlesinger[23] also concluded that calcific

aortic stenosis may be the result of a pure arteriosclerotic process. Ashworth[24] described the earliest change in the calcific aortic valve as an extracellular deposit of lipid material with cholesterol crystals. Calcific masses appeared at the sites of previous lipid deposits. Hutgren[25] made a study of the aortic valves in 100 consecutive unselected autopsies of adults. Calcium deposits were found in the aortic valves of forty-six hearts. In thirty-four of these there was no gross or microscopic evidence of rheumatic valvular disease. Calcium deposits occurred more frequently and were larger in anount in the older age groups. Microscopic study revealed alterations in the dense connective tissue at the base of the valve leaflet and in the fibrosa layer of the valve. There was deposition of fatty material with masses of closely packed needle-shaped clefts beneath the endocardium. He concluded that in many cases calcification of the aortic valve results from a purely degenerative process and not from a rheumatic inflammatory process. Karsner and Koletsky[16] stated that occasionally lipids are present in the lesion and that xanthoma cells occur at the periphery of the calcific mass. Margolies and his associates[27] noted that an acellular, often hyalinized, fibrous tissue surrounded the calcareous material and that within this, particularly at the margin of the calcareous nodules, there were variable amounts of lipoid material, sometimes in large globules.

If calcific aortic stenosis is atherosclerotic in origin, one should find atherosclerosis of the aorta and of the coronary arteries associated with the valvular lesions. Evidence for the frequency of this association is conflicting. Margolies and his associates[27] found coronary sclerosis in all of their cases, as did Anderson and co-workers.[28] Coronary sclerosis was moderate or marked in degree in one-half of Margolies' and on one-fourth of Anderson's cases. Kumpe and Bean[3] reported that coronary arteriosclerosis is common in subjects of aortic stenosis and Lesnick and Schlesinger[23] found more coronary sclerosis in cases of "pure" aortic stenosis than in those of rheumatic origin. A number of authors have claimed that the degree of aortic and coronary atherosclerosis is in inverse proportion to the tightness of the aortic stenosis, as though the aortic narrowing protected the aorta and coronary arteries from the full force of the systolic ejection of the blood. But the evidence for this is not altogether convincing. Karsner and Koletsky state that aortic stenosis does not spare the proximal aorta from atherosclerosis, but Clawson and his associates[29] found the arch of the aorta smooth, the rest of the vessel sclerotic. Dry and Willius[30] observed that sclerosis of the aorta and coronary arteries was less, the tighter the aortic stenosis. Horan and Barnes[31] made similar observations, although they found some degree of coronary sclerosis in every case.

It appears to us from this survey of pathologic studies that calcific aortic stenosis may develop as a pure atherosclerotic process. But a more important point seems to be the fact that in the majority of cases of calcific aortic stenosis, even when the lesion was initiated by a rheumatic valvulitis, the final major valvular deformity is the result of a secondary atherosclerosis of the scarred valve leaflet. This has been suggested by Sohval and Gross and by Anitschkow. The process is quite analogous to the atherosclerosis that develops in arteries following an episode of arteritis[32] in vessels damaged by thromboangiitis ob-

literans; or, in the experimental field, to the localization of experimental atherosclerosis in segments of arteries that have been first traumatized in some manner.

Twenty-three per cent of the patients with aortic stenosis had a definite history of rheumatic fever. Another 47 per cent had known of the existence of a murmur for 10 or more years. These murmurs most probably arose as a result of previous rheumatic infection. Based on their history 70 per cent of the patients in our sample with aortic stenosis probably had had rheumatic valvulitis. Applying the same criteria to patients with rheumatic valvular disease we found that 82 per cent gave evidence of previous rheumatic infection. It seems clear, therefore, that the lesion of aortic stenosis is commonly initiated by a rheumatic infection and that the scarred valve leaflets favor the localization of a secondary atherosclerosis that ultimately may lead to the valvular deformity of calcific aortic stenosis. It is quite probable that similar processes occur on the mitral valve, but we have no data to support this hypothesis.

Many facts support the view that rheumatic valvulitis is not the sole cause of aortic stenosis.

Calcific aortic stenosis usually develops late in life. Persons who have had rheumatic fever in childhood or youth, with the development of a valvular lesion, may remain symptom-free for years with no rheumatic recrudescences and no cardiac complaints and finally late in life may develop signs of aortic stenosis. Other forms of rheumatic valvular disease do not progress in this manner.

Atherosclerosis of the aorta and of the coronary arteries occurs in most persons with calcific stenosis. Angina pectoris is very common among them. It is probably caused by the combined effect of the aortic and coronary stenosis on the coronary blood flow. Great narrowing of the aortic orifice may induce angina pectoris in the absence of coronary sclerosis or with minimal coronary sclerosis. Lesser degrees of stenosis cause anginal pain only when there is a greater degree of coronary sclerosis.

Most telling is the occurrence of calcific aortic stenosis in persons with familial xanthomatosis and hypercholesteremia, even in the absence of rheumatic infection. Several such cases have been observed in children, and we have seen one case in a young man aged 20.

Finally our studies of the serum cholesterol in patients with aortic stenosis suggest that in some cases atherosclerosis may be an element in the genesis of the lesion. About 50 per cent of the women had significant elevation of serum cholesterol levels. The difference between the sexes follows the usual pattern of atherosclerosis. It is common knowledge that atherosclerosis is much more frequent in men than in women and that in most women under age 60 atherosclerosis rarely develops in the absence of some contributory factor such as diabetes, hypertension, or familial hypercholesteremia. It may be that women are unlikely to develop primary or secondary atherosclerosis of the aortic valve unless the process is favored by an existing hypercholesteremia.

SUMMARY

The serum cholesterol of eighty-six patients with aortic stenosis, forty-three men and forty-three women, and of sixty-seven patients with chronic rheumatic valvular disease, twenty-two men and forty-five women, was determined. Using Keys' standards, 48.8 per cent of the females and 18.6 per cent of the males with aortic stenosis were hypercholesteremic, whereas of those with chronic rheumatic valvular disease 13.3 per cent of the females and 13.6 per cent of the males were hypercholesteremic. By using standards derived from a study of a random sample of a union population in New York City (The Amalgamated Clothing Workers of America), 53.5 per cent of the females and 27.9 per cent of the males with aortic stenosis were hypercholesteremic; and of those with rheumatic valvular disease 20 per cent of the women and 18.2 per cent of the men were hypercholesteremic.

Of the patients with aortic stenosis 70 per cent apparently had had previous rheumatic infection.

Three patients with xanthomatosis and hypercholesteremia and one with familial hypercholesteremia who also had aortic stenosis were observed. Only one of these had had rheumatic fever. One was a man aged 20.

Our material favors the hypothesis that in persons with hypercholesteremia aortic stenosis may be caused by atherosclerosis of a normal aortic valve, but that in most instances it is caused by a secondary atherosclerosis implanted on aortic cusps scarred by ancient rheumatic infection.

We wish to express our thanks to Dr. F. H. Epstein and Mrs. R. Simpson for preparing and making available to us the data of the Hillman Health Center, to Dr. Arthur G. Steinberg for assistance in computing and evaluating the statistical data of this paper, and to Miss Sarah J. Baker and Miss Helen Fung for technical assistance.

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CALCIFICATION OF THE MITRAL VALVE ANNULUS AND ITS RELATION TO FUNCTIONAL VALVULAR DISTURBANCE

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THE occurrence of variable degrees of calcification of the mitral valve annulus is well known to clinician and pathologist. As the life span in the general population increases, this lesion is now more often encountered at necropsy and may not be entirely without clinical interest and significance.

Prominent clinicians[1-5] dismiss calcification of the mitral valve annulus somewhat vaguely as occasionally associated with an apical systolic murmur and possible mitral regurgitation. Only a few authors[6,7,16] admit the possibility that this lesion may produce mitral stenosis. When calcification of the mitral annulus is minimal and focal in character, not only may it be overlooked in routine autopsies, but it is doubtful whether any significance can or should be attached to it. It is only when calcification is marked or extensive that it may assume functional significance. To study this point, this investigation was undertaken.

MATERIAL AND METHODS

Five hundred and ninety unselected autopsy protocols were reviewed and the incidence of calcification of the mitral annulus, both gross and microscopic, was noted. The age, sex, degree of calcification, heart weight, evidence of the presence of rheumatic heart disease, the presence of dilatation and/or hypertrophy of the left auricle, additional valvular involvement, and the clinical diagnosis of functional mitral valvular disease, were noted. The clinical findings with particular reference to heart murmurs were reviewed.

RESULTS

Calcification of the mitral valve annulus was found in fifty-nine hearts giving an over-all incidence of 10 per cent. This incidence is actually greater in an adult population. Thus, in this series, if 119 autopsies on individuals under 10 years of age are excluded, the percentage in an adult population rises to 12.5 per cent. This is slightly higher than the incidence of 10 per cent reported by Fertman and Wolff.[8]

The average age of individuals in this series showing calcification of the mitral annulus was 69 years, only one case occurring at 50 years of age. The ages ranged from 50 to 90 years. While of more frequent occurrence in females (36) than in males (23), the 2:1 ratio reported by Fertman and Wolff[8] was not

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Received for publication May 7, 1954.

TABLE I. CASES SHOWING VARIABLE DEGREES OF DILATATION AND/OR HYPERTROPHY OF LEFT AURICLE IN MITRAL ANNULUS CALCIFICATION

CASE NO.	MITRAL MURMURS		CLINICAL DIAGNOSIS OF MITRAL DYSFUNCTION	MURMURS OF OTHER VALVULAR DISEASE	AORTIC VALVE CALCIFICATION PRESENT	CARDIAC ARRHYTHMIA PRESENT	HISTORY OF FINDINGS OF RHEUMATIC HEART DISEASE
	DIASTOLIC	SYSTOLIC					
1. A-1346 (70082)	No	Yes (Soft)	No	None	Yes	No	No
2. A-1566 (81072)	Yes	Yes	Regurgitation	Aortic systolic and diastolic	No	Auricular fibrillation	No
3. A-1486 (76782)	No	Yes	No	No	No	Sinus tachycardia	No
4. A-1434 (74801)	Yes	Yes (Loud)	No	No	Yes	Left bundle branch block	No
5. A-1807 (96668)	No	No	No	No	Yes	No	No
6. A-1788 (95313)	Yes (Short)	Yes (Loud)	No	No	Yes	Auricular fibrillation	No
7. A-1756 (93720)	No	Yes (Musical)	No	Aortic systolic	No	Auricular fibrillation	No
8. A-1834 (97032)	No	No	No	No	No	No	No
9. A-1832 (98090)	No	Yes	Regurgitation	Aortic systolic and diastolic	Yes	Sinus tachycardia	Yes
10. A-1265 (65959)	No	No	No	No	No	Auricular fibrillation	No
11. A-1297 (67793)	No	No	No	No	Yes	Complete A-V block	No

observed in this series. The average weight of the heart of subjects showing mitral annulus calcification was 454 grams with weights ranging from 760 to 275 grams. It is to be noted that this average increase in heart weights is not to be interpreted as hypertrophy due to mitral valve dysfunction, but rather as hypertrophy associated with a variety of pathologic cardiac conditions found in this series, the most frequent being variable degrees of coronary arteriosclerosis and hypertension. It is interesting to note that sixteen cases (approximately 27 per cent) exhibited variable degrees of aortic valve calcification with variable degrees of stenosis and that this associated aortic valve lesion occurred three times as frequently in women (12) as in men (4). In only three cases showing mitral annulus calcification was a diagnosis of rheumatic heart disease made pathologically.

Of the fifty-nine cases showing calcification of the mitral annulus, fourteen (as indicated in the autopsy protocols) showed some degree of dilatation and/or hypertrophy of the left auricle. Since dilatation and/or hypertrophy of the left auricle was taken as the best available, and perhaps most reliable, objective evidence of possible significance of mitral valve dysfunction (either stenosis or regurgitation), the clinical data of this group of cases were carefully scrutinized for the presence or absence of cardiac murmurs. The findings in this group are summarized in Table I.

In the group of eleven subjects with variable degrees of mitral annulus calcification who showed some degree of dilatation and/or hypertrophy of the left auricle (Table I) and in whom clinical data were available, seven cases (63.6 per cent) exhibited an apical mitral systolic murmur. Only one of these (Case 9) had evidence of rheumatic heart disease. In this case, only minimal rheumatic thickening of the leaflets was present, while the annulus calcification was marked. In three of these seven cases (Cases 4, 6, and 7), the mitral apical murmur was described as being either loud or musical, i.e., having special qualities, but no mention of the character of the systolic murmurs in the other cases was made.

In this group of eleven cases, associated calcification of the aortic valve leaflets was present at autopsy in six instances and occurred in four of the cases (Cases 1, 4, 6, and 9) in which mitral apical systolic murmurs were heard, but in only one (Case 9) of these four was an aortic murmur present. Calcification of the aortic valve was associated in one other patient (Case 11) in whom no mitral apical systolic murmur was present. On the other hand, it is interesting to note that the murmurs heard over the aortic areas and recorded in two instances (Cases 2 and 7) failed to show anatomic evidence of calcification of the aortic valve, although in these cases a mitral apical systolic murmur was present. Two instances of heart block (Cases 4 and 11) were noted. The clinical diagnosis of mitral regurgitation was made in two instances (Cases 2 and 9). In only three instances were presystolic (diastolic) murmurs recorded.

In a group of thirteen cases a mitral apical systolic murmur was heard in eight instances (61.5 per cent), thus indicating that mitral apical systolic murmurs occur with the same frequency in mitral annulus calcification without hypertrophy or dilatation of the left auricle as in those showing left auricular

TABLE II. CASES SHOWING MARKED MITRAL ANNULUS CALCIFICATION WITHOUT EVIDENCE OF LEFT AURICULAR HYPERTROPHY OR DILATATION

CASE NO.	MITRAL MURMURS		CLINICAL DIAGNOSIS OF MITRAL DYSFUNCTION	MURMURS OF OTHER VALVULAR DISEASE	AORTIC VALVE CALCIFICATION PRESENT	CARDIAC ARRHYTHMIA PRESENT	HISTORY OR FINDINGS OF RHEUMATIC HEART DISEASE
	DIASTOLIC	SYSTOLIC					
1. A-1746 (93281)	No	Yes (Loud)	No	Systolic, whole precordium	Yes	Auricular fibrillation	No
2. A-1678 (88987)	No	No	No	No	No	Sinus tachycardia	No
3. A-1636 (86584)	No	No	No	No	No	Auricular fibrillation	No
4. A-1576 (82146)	No	Yes (Loud)	Regurgitation	No	Yes	Auricular fibrillation	No
5. A-1499 (77207)	? Presystolic	Yes (Loud)	Calcified mitral valve and ring with regurgitation	Aortic systolic	No	Sinus tachycardia	No
6. A-1367 (71016)	No	Yes (Loud)	No	No	No	Auricular fibrillation, right bundle branch block	No
7. A-1345 (69924)	No	No	No	No	Yes	No	No
8. A-1315 (68620)	No	No	No	Aortic systolic	No	Auricular fibrillation	No
9. A-1308 (67837)	No	No	No	No	No	No	No
10. A-1293 (67624)	No	Yes (Rough)	No	Systolic, whole precordium	No	No	No
11. A-1294 (67485)	No	Yes (Soft)	No	Aortic systolic	No	No	No
12. A-1743 (O.S.P.)	Slight pre-systolic	Yes (Loud)	Regurgitation	Systolic, whole precordium	Yes	No	No
13. A-1698 (73408)	No	Yes (Short)	No	Systolic, whole precordium	No	No	No

enlargement. In six of the eight cases (Cases 1, 4, 5, 6, 10, and 12) included in Table II, the apical systolic murmur was described as loud or rough. A questionable presystolic murmur was heard in two instances, and a clinical diagnosis of mitral regurgitation was made three times (Cases 4, 5, and 12). In this group of cases, aortic valve calcification was noted four times and was present in two cases (Cases 4 and 7) in which no mention of murmurs being heard in the aortic area was recorded.

Thus, in a total of twenty-four cases of calcification of the mitral valve annulus, (Tables I and II), apical systolic murmurs referable to the mitral valve were heard in fifteen subjects (62.5 per cent) and nine of these had murmurs of special quality (loud, rough or musical). A clinical diagnosis of mitral regurgitation was made five times (33.3 per cent) in these fifteen patients.

DISCUSSION

Although calcification of the mitral valve annulus may be associated with rheumatic heart disease, most investigators[9-13] regard the fibrous thickening, lipid deposition, calcification and even osseous metaplasia of the mitral annulus as a pure degenerative change, similar, in many respects, to arteriosclerosis. It is rarely seen in significant degrees in persons under 50 years of age.

When present in a marked degree, it is a linear, J- or U-shaped lesion involving mainly the fibrous tissue of the annulus of the posterior mitral valve leaflet. It rarely extends into the base of the leaflet itself but rather lifts the leaflet. The calcification may extend downward into the myocardium of the left ventricle (Figs. 1 and 2) and may extend into the interventricular septum where, occasionally, it may interfere with the conduction system.[13,14] The calcified annulus may reach dimensions of 2 cm. or more in diameter and form a rigid, angulated shelf over which the leaflet may be relatively unaltered, being smooth, pliable and not shortened. It is difficult to conveive that a pathologic change of such magnitude, situated in such a strategically important area, can be present without producing some degree of valvular dysfunction.

In the light of the newer knowledge concerning the method and mechanics of closure of the mitral valve,[15] the location and degree of mitral annulus calcification take on importance and significance. In the bloodless heart preparation as devised by Dr. Adrian Kantrowitz of the Montefiore Hospital of New York,[15] it is remarkable to see how much ring movement actually takes place. In diastole, the valve ring and valve cusps are open. In systole, there is a rhythmic sphincter-like contraction of the entire mitral ring which narrows considerably the size of the lumen which the mitral cusps must bridge to complete closure of the valve (Fig. 3). This is of considerable importance because the size of the gap that has to be bridged is really much smaller than one would assume, since it is made much smaller by the contraction of the valvular ring. The contraction of the ring is muscular while the closure of the leaflets is hydrodynamic and depends upon the pressure of fluid in the left ventricle.

Under these circumstances, there can be little doubt that mitral annulus calcification, when present in considerable degree, presents a rigid, noncom-

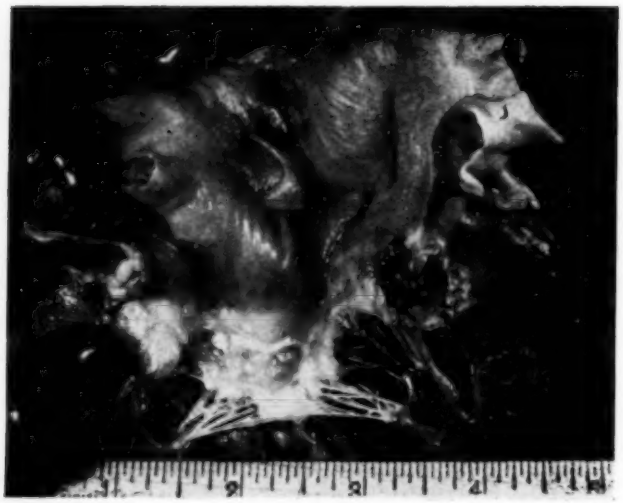

Fig. 1.—Heart opened to expose mitral valve and annulus. Note massive calcification of annulus on left cut edge. The mitral valve shows no evidence of rheumatic endocarditis.

Fig. 2.—Low-power microscopic view of left auricle, (upper left), calcified mitral annulus, and posterior mitral valve leaflet. Note extension of calcification of annulus into left ventricular musculature.

pressible U- or J-shaped segment of the ring which will not permit as much reduction in the gap to be bridged by the mitral leaflets as is produced in the normal valve. Since in complete closure, the mitral leaflets overlap, the failure of sufficient reduction of the gap by ring contraction may lead to a relative or frank mitral regurgitation. It is interesting to note that Fishberg,[16] who subscribes to this concept of the production of mitral regurgitation in mitral annulus calcification, pointed out that Roy and Adami (quoted by Fishberg[16]) in 1894 had observed the circumference of the mitral orifice during systole to be only one-half of that during diastole.

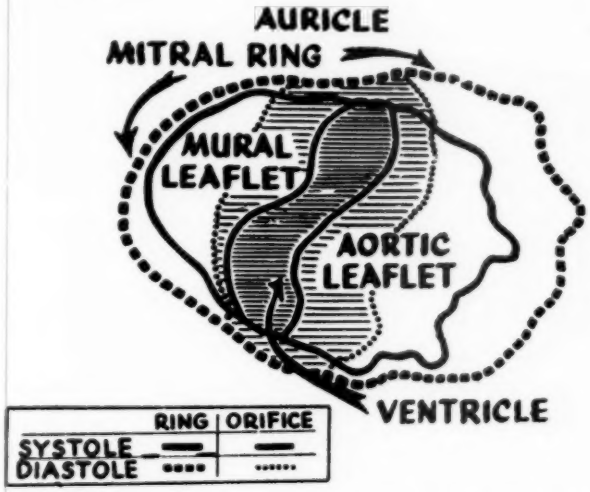

Fig. 3.—Schematic diagram showing the degree of closure of the mitral ring produced by systolic musculature contraction of ring before hydrostatic closure of mitral leaflets. The area to be bridged by the valve leaflets is reduced approximately to one-half by this muscular contraction.

The apical systolic murmurs referable to the mitral valve which were present in 62.5 per cent of the twenty-four cases in which the clinical data were scanned (Tables I and II), are difficult to evaluate since the quality of the murmurs, their transmission and, above all, the experience of the observing physician were often not recorded and could not be assessed.

Although mitral regurgitation is a commonly given explanation for a systolic murmur confined to the apex, many apical systolic murmurs are frequently encountered and dismissed by many competent physicians as so-called functional, nonorganic murmurs. Such so-called functional murmurs are said to be soft in quality and are not transmitted to the axilla. It is only when the apical systolic murmur is loud, rough, or musical, and is transmitted to the axilla that functional significance, e.g., mitral regurgitation, is implied by the murmur. Such loud, rough or musical apical systolic murmurs were present in Cases 4, 6, and 7 of Table I, and in Cases 1, 4, 5, 6, 10, and 12 of Table II. These nine cases appear to be acceptable as exhibiting types of murmur which could be attributed to mitral regurgitation. It is interesting to note that in these nine cases, the clinical diagnosis of mitral regurgitation was made three times (Cases 4, 5, and 12, Table II). The clinical diagnosis of mitral regurgitation was made

in two other instances (Cases 2 and 9, Table I), in which the character of the systolic murmur is not described other than to indicate its presence. Although Libman[17] suspected the presence of mitral annulus calcification upon hearing a systolic murmur along the left sternal border, Rytand and Lipsitch[18] did not regard the murmurs in their cases of mitral annulus calcification as evidence of either mitral regurgitation or of mitral stenosis.

In five of the nine cases (Cases 4 and 6, Table I, and Cases 1, 4, and 12, Table II) which exhibited apical systolic cardiac murmurs with the special qualities noted, there was associated calcification of the aortic valve at autopsy. In only one of these five cases (Case 12, Table II) was a clinical diagnosis of aortic valve dysfunction made. This suggests that the murmurs heard at the aortic area were possibly regarded as insignificant or as being transmitted from the mitral area, rather than as murmurs originating in the aortic valve. These findings suggest that although variable degrees of aortic calcification are frequently found associated in hearts with mitral annulus calcification, the majority of systolic murmurs heard at the aortic area are not interpreted as being produced by calcification of the aortic valve and ring but are considered to originate at the mitral valve and to be referred to the aortic area.

In regard to presystolic or diastolic murmurs heard at the mitral area, these were noted as being present in only five subjects (Cases 2, 4, and 6, Table I, and Cases 5 and 12, Table II). In none of these was a clinical diagnosis of mitral stenosis made. It would appear, therefore, that considerable degrees of mitral annulus calcification do not produce the characteristic murmur which leads to a clinical diagnosis of mitral stenosis. While presystolic or diastolic murmurs may possibly be produced by blood flowing over the jutting angulation produced by the mitral annulus calcification, frank mitral stenosis, as such, is probably not produced by this lesion.

SUMMARY AND CONCLUSIONS

Calcification of the mitral valve annulus is not infrequent. Its incidence was 10 per cent in 590 unselected, consecutive autopsies on subjects of all ages. The incidence was higher in individuals over 50 years of age.

While calcification of the annulus of the mitral valve may occur in rheumatic heart disease, it is primarily a degenerative process similar, in many respects, to arteriosclerosis. In the majority of cases the process does not affect the mitral valve leaflets.

Variable degrees of calcification of the aortic valve, presumably on a nonrheumatic basis, were associated in approximately 25 per cent of the subjects whose hearts showed calcification of the mitral valve annulus.

In a selected series of twenty-four cases of mitral annulus calcification, apical systolic murmurs presumably referable to the mitral valve, were heard in fifteen cases (62.5 per cent). In nine of these fifteen cases (60.0 per cent) the quality of the murmurs was such (loud, rough, or musical) as may be associated with functional derangement at the mitral orifice, and in five instances, 33.3 per cent, a clinical diagnosis of mitral regurgitation was made.

In the light of our newer knowledge of the mechanics of the closure of the mitral valve, it is suggested that extensive calcification of the mitral valve annulus

interferes with the rhythmic muscular contraction of the mitral ring by forming a rigid, noncompressible segment of that ring. Thus, the gap to be bridged may not be sufficiently reduced to permit the overlapping closure by the mitral leaflets.

This concept of interference with contraction of the valve ring, together with the observation that 60 per cent of apical systolic murmurs in our proved cases of mitral annulus calcification have special qualities suggesting mitral dysfunction, is construed as presumptive evidence that extensive mitral annulus calcification (without rheumatic involvement of the leaflets) may produce relative or frank mitral regurgitation.

Whether such mitral regurgitation, either relative or frank, as may be produced by mitral annulus calcification is sufficient to further impair the cardiac function of subjects in an older age group, the majority of whose hearts are already partially damaged, is extremely difficult to assess, and is beyond the scope of this paper.

Extensive calcification of the mitral valve annulus which may produce variable degrees of mitral regurgitation can be strongly suspected in individuals over 50 years of age having loud, rough, or musical systolic apical murmurs who give no history of previous rheumatic heart disease.

The authors wish to express their thanks to Dr. Harold N. Segall for his aid, interest, and many helpful suggestions regarding the interpretations and significance of the cardiac murmurs encountered in the study of these cases.

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BIOPSIES OF THE LUNG AND ATRIAL APPENDAGES IN MITRAL STENOSIS: CORRELATION OF DATA FROM CARDIAC CATHETERIZATION WITH PULMONARY VASCULAR LESIONS

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THIS study was undertaken to determine the character and incidence of lesions in a series of twenty-five lung biopsy specimens, which were obtained from rheumatic patients at the time of mitral commissurotomy, for correlation with physiologic data provided by cardiac catheterization. The pulmonary vascular changes associated with rheumatic heart disease have been described in autopsy material,[1-4] but only the recent reports of Enticknap[5] and Clowes and his associates[6] are concerned with systematic physiopathologic investigations of living patients. The clinical significance of the pulmonary vascular lesions still merits attention. The pathologic findings in seventy-five surgically resected left atrial appendages also are summarized.

LUNG STUDIES

Material and Methods.—The physiologic data obtained at the time of venous cardiac catheterization prior to mitral commissurotomy in twenty-three patients were evaluated with particular reference to the degree of the thickening of the walls of the intrapulmonary vessels. The pulmonary arterial pressure, pulmonary "capillary" pressure, cardiac index, and the arteriovenous oxygen difference were determined at rest in all patients. In eighteen cases, the response to exercise was evaluated by the determination of these data; satisfactory pulmonary "capillary" pressures were not obtained in the remaining five patients. A summary of these values, together with an appraisal of the pulmonary vascular alterations, is presented in Table I.

Cardiac catheterization was performed by the usual technique with pressures determined by means of Statham strain gauges and a Hathaway recording apparatus. The zero reference point was 10 cm. above the patient's back. Blood gas determinations were made by the Van Slyke-Neill manometric mechod,[7] and respiratory gas determinations were performed according to the Scholander technique.[8]

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This study was supported (in part) by the United States Public Health Research Grant (H-1208).
Received for publication Feb. 5, 1954.

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The lung specimens were all removed from the lingula at the time of operation, fixed in formalin, and embedded in paraffin. Hematoxylin and eosin, elastic fiber-van Gieson, and Gomori rapid trichrome stains were used routinely. Sections from most of the specimens were stained for iron. For use in Table I,

Fig. 1.

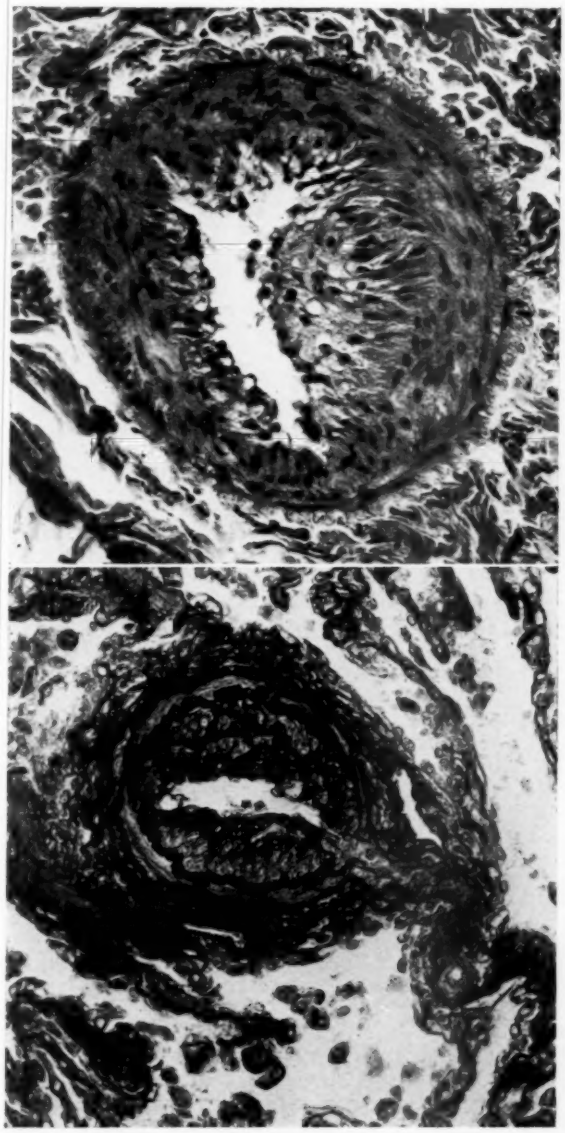

Fig. 2.

Fig. 1.—Hypertrophy of media and vacuolated fibrous intimal proliferation of artery. (Hematoxylin-eosin stain; ×250.)

Fig. 2.—Advanced arterial intimal fibrosis and extensive elastic fiber proliferation. (Elastic fiber-von Gieson stain; ×250.)

TABLE I. PHYSIOLOGIC DATA*

NO.	SEX-AGE (YR.)	DURATION OF SYMPTOMS (YR.)	CLASS	PHYSIOLOGIC STATE	PHYSIOLOGIC DATA							PATHOLOGY		CLINICAL RESULTS	COMMENT
					PULMONARY ART. PRESS. MEAN (MM. HG)	PULMONARY "CAPILLIARY" PRESS. (MM. HG)	CARDIAC OUTPUT	CARDIAC INDEX	TOTAL PUL. ART. RESISTANCE DYNES SEC./CM.$^{-5}$	PUL. ARTERIOLAR RESISTANCE DYNES SEC./CM.$^{-5}$	PER CENT RISE PUL. ARTERIOLAR REST. ON EX.	PULMONARY ARTERIAL	PULMONARY ARTERIOLES		
1	FE 39	5	IV	Rest	61	24	3010	2.17	1620	983		Sev.	Sev.	Good	"Tight" mitral stenosis functional tricuspid insuff.
				Ex.	90	30	2670	1.79	2700	1800	101				
2	M 29	2	IV	Rest	74	27	5380	2.8	1100	699		Sev.	Sev.	Fair	"Tight" mitral stenosis functional tricuspid insuff.
				Ex.	99	35	4790	2.0	1656	1070	53				
3	FE 32	8	III	Rest	56	27	3610	2.8	1242	645		Sev.	Sev.	Good	"Tight" mitral stenosis
				Ex.	77	39	5100	4.0	1207	597	−8				
4	FE 25	3	III	Rest	50	23	3550	2.65	1125	608		Mild	Mod.	Exc.	"Tight" mitral stenosis
				Ex.	80	35	3530	2.63	1810	1020	68				
5	M 38	4	IV	Rest	60	27	4390	2.4	1095	601		Mod.	Mod.	Fair	"Tight" mitral stenosis functional tricuspid insuff.
				Ex.											
6	FE 39	10	III	Rest	34	13	3590	2.2	757	467		Mild	Mod.	Fair	"Tight" mitral stenosis
				Ex.	37	21	4440	2.7	666	288	−62				
7	FE 49	5	III	Rest	40	23	3420	2.4	937	398		Mod.	Mod.	Exc.	"Tight" mitral stenosis
				Ex.	68	44	4420	3.3	1230	434	11				
8	M 36	6	III	Rest	40	22	3620	1.9	884	397		Abs.	Abs.	No change	Not a surgical mitral stenosis predom. mitral insuff.
				Ex.	78	37	4140	2.2	1507	792	100				
9	FE 43	14	III	Rest	38	24	3090	2.06	983	362		Mod.	Mod.	Fair	"Tight" mitral stenosis
				Ex.	41	25	3520	2.34	931	363	0				
10	FE 20	1	II	Rest	44	28	4130	2.7	850	309		Mod.	Mod.	Exc.	"Tight" mitral stenosis
				Ex.											
11	FE 41	6	III	Rest	24	14	2750	1.7	697	290		Mild	Mod.	Fair	"Tight" mitral stenosis functional tricuspid insuff.
				Ex.	44	24	5580	3.4	630	286	0				

	20			Ex.											
11	FE 41	6	III	Rest	24	14	2750	1.7	697	290		Mild	Mod.	Fair	"Tight" mitral stenosis functional tricuspid insuff.
				Ex.	44	24	5580	3.4	630	286	0				
12	FE 33	4	III	Rest	48	32	4860	3.2	787	262		Mild	Mod.	Good	"Tight" mitral stenosis
				Ex.	63	37	4500	3.0	1120	461	76				
13	FE 18	3	III	Rest	26	12	4320	2.9	484	259		Abs.	Mild	Good	"Tight" mitral stenosis
				Ex.	36	20	6490	4.6	414	195	−33				
14	FE 42	7	III	Rest	39	20	3740	2.6	834	235		Mild	Mild	Fair	"Tight" mitral stenosis
				Ex.	60	32	6020	4.1	795	372	58				
15	FE 43	12	IV	Rest	29	19	4120	2.2	562	194		Mild	Mod.	Good	"Tight" mitral stenosis tricuspid sten.; M&T valvulotomy
				Ex.	34	22	5120	2.7	531	187	−4				
16	FE 18	1	II	Rest	40	27	5500	3.9	582	190		Mild	Mod.	Exc.	"Tight" mitral stenosis
				Ex.											
17	FE 32	4	III	Rest	37	29	3430	2.2	861	186		Mod.	Mod.	Fair	"Tight" mitral stenosis
				Ex.											
18	FE 35	7	III	Rest	31	24	3500	2.26	708	160		Mild	Mod.	Good	"Tight" mitral stenosis
				Ex.	61	40	4670	3.0	1044	361	125				
19	M 21	5	III	Rest	34	26	6030	3.25	451	106		Mild	Mod.	Exc.	"Tight" mitral stenosis
				Ex.	101	34	8420	4.56	960	636	500				
20	M 32	5	III	Rest	25	19	5282	2.7	378	91		Mild	Mild	Good	"Tight" mitral stenosis
				Ex.											
21	FE 39	5	III	Rest	20	15	5110	2.8	313	79		Mod.	Mod.	Fair	"Tight" mitral stenosis
				Ex.	32	22	7800	4.6	328	103	30				
22	FE 20	1	III	Rest	19	14	5540	3.7	274	73		Abs.	Abs.	Exc.	"Tight" mitral stenosis
				Ex.	28	19	6780	4.5	330	107	49				
23	FE 40	20	III	Rest	25	21	4980	3.5	401	64		Mod.	Mod.	Good	"Tight" mitral stenosis
				Ex.	28	21	4960	3.49	452	113	76				

*The functional capacity of patients is based on criteria outlined in *Nomenclature and Criteria for Diagnosis of Diseases of the Heart*, New York Heart Association, Inc., 1946.

the structural changes in the muscular arteries and arterioles were graded as absent, mild, moderate, and severe. "Mild" lesions consisted of definite but slight nonobstructive thickening of the wall. The term "moderate" was applied when at least one-half of the vessels in the section showed pronounced mural thickening, but the breadth of the wall seldom exceeded the diameter of the lumen. "Severe" changes were more or less obstructive; the lumina of many vessels appeared narrower than the thickness of the wall. The muscular arteries were those whose elastic components normally include only internal and external laminae. The vessels which were designated as arterioles were the smaller arterial branches that have a single elastic membrane and no muscular component, or at most a single layer of muscle fibers in the wall. The precapillaries were included with the arterioles.

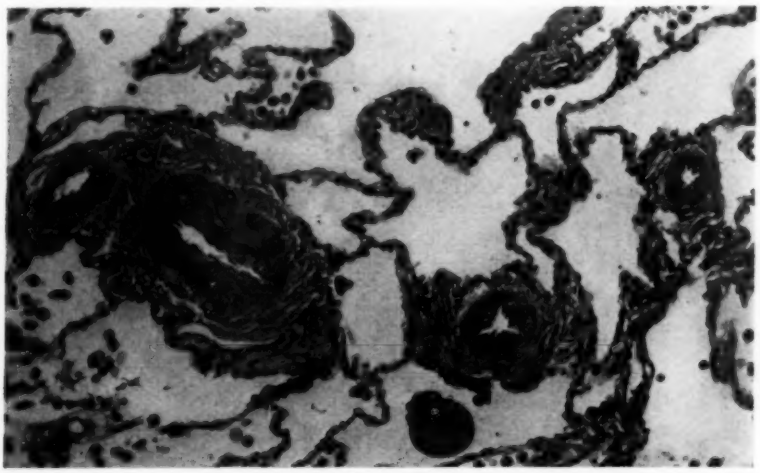

Fig. 3.—A group of small arteries with severe intimal fibrosis. (Hematoxylin-eosin stain; ×150.)

HISTOLOGIC OBSERVATIONS

Patients With Mitral Stenosis.—Intimal alterations were commonplace. The earliest change in the larger arteries consisted of a thin growth of radially arranged intimal fibers with dark oval nuclei. These fibers were often separated by transparent vacuoles. They blended with the internal elastic membrane and tended to take the stain for elastic fibers (Fig. 1). The medium-sized and smaller muscular arteries showed varying degrees of concentric or slightly eccentric nonverrucous fibrous intimal thickening. This intimal tissue was fibrillary or dense, and most of it appeared to be young connective tissue, which stained yellow with the van Gieson method and did not show evidence of hyalinization. A scattering of dark nuclei, which were smaller than those of the medial muscle fibers, was usually present. In the more sclerotic vessels, minute patches of mature collagen were present. The internal elastic membrane was splintered, and ultimately a network of fine and coarse fibers developed throughout the entire wall. The external elastica showed splitting less often, but the adventitia occasionally contained large amounts of elastic tissue (Fig. 2). As the intima

Fig. 4.

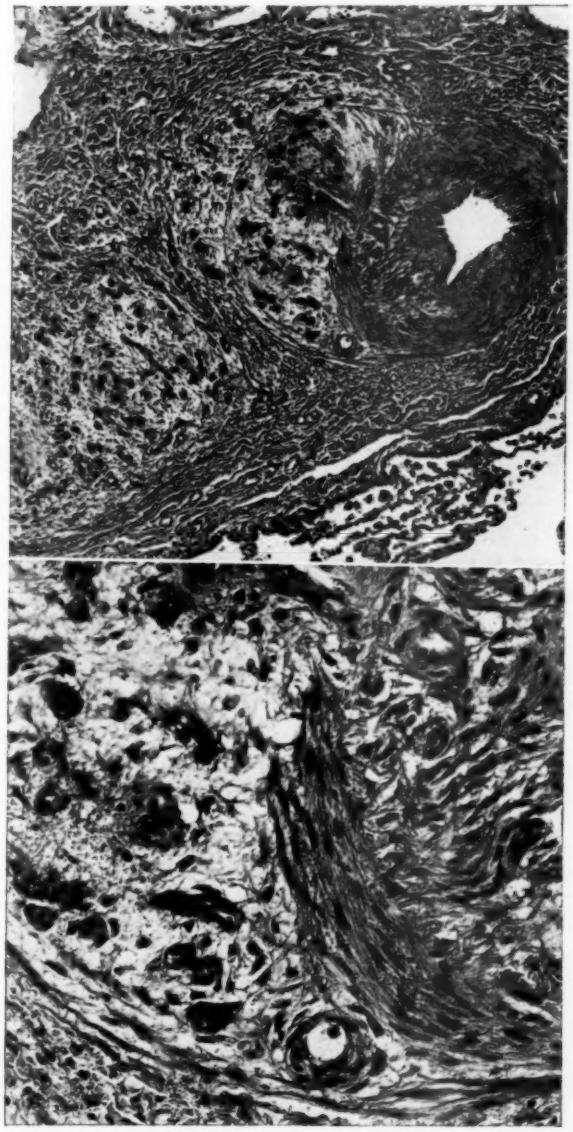

Fig. 5.

Fig. 4.—Granulomatous nodular lesion within and adjacent to the arterial wall. (Hematoxylin-eosin stain; ×75.)

Fig. 5.—Higher magnification of vessel in Fig. 4 showing disruption of the hypertrophic media at the right by vacuolated mucoid material containing endothelial channels. (Hematoxylin-eosin stain; ×250.)

proliferated, the media became correspondingly compressed and moderately atrophic (Fig. 3). The endothelium was sometimes swollen, but it did not proliferate. Necrosis, deposition of fibrin within the intima, or infiltration of the wall with leukocytes were not observed.

The media appeared thickened in eight cases, mainly because of muscular hypertrophy, but possibly also because of contraction of the vessel. While muscular hypertrophy did not appear especially prominent in the majority of sections, it was rather impressive in comparison with the control cases. Mild foamy vacuolation was noted occasionally between the muscle fibers of the media. In several arteries of three cases, the muscle fibers were disoriented, scattered, or whorled.

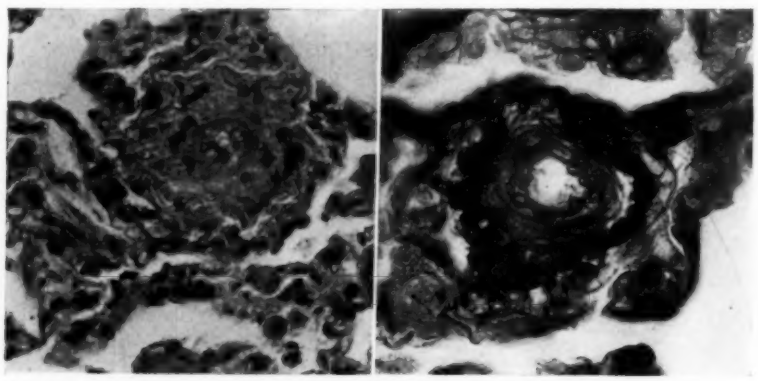

Fig. 6. Fig. 7.

Fig. 6.—An arteriole with occluded lumen and thickened wall. (Hematoxylin-eosin stain; ×300.)

Fig. 7.—Arteriole with obstructive proliferation of delicate connective tissue inside the elastic membrane. (Elastic fiber-von Gieson stain; ×450.)

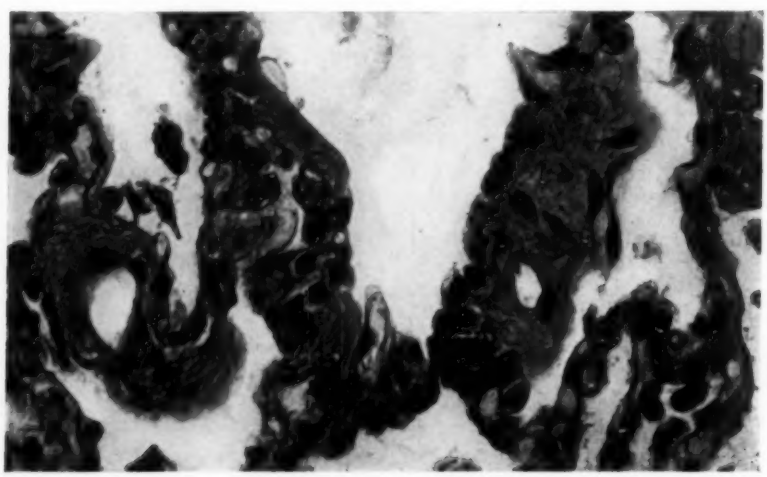

Fig. 8.—Patchy fibrosis of alveolar septa with thickening of walls of precapillary vessels. (Hematoxylin-eosin stain; ×450.)

In one case, the arteries exhibited large nodular lesions (Figs. 4 and 5). Patchy areas of the hypertrophic media and the greatly widened fibrous adventitia were disrupted by fields of vacuolated blue mucinous material through which many capillary channels and a few fibroblastic nuclei had proliferated. This productive reaction occasionally extended inward, rather than outward, to replace the intima partially. Almost no accompanying leukocytic reaction was present.

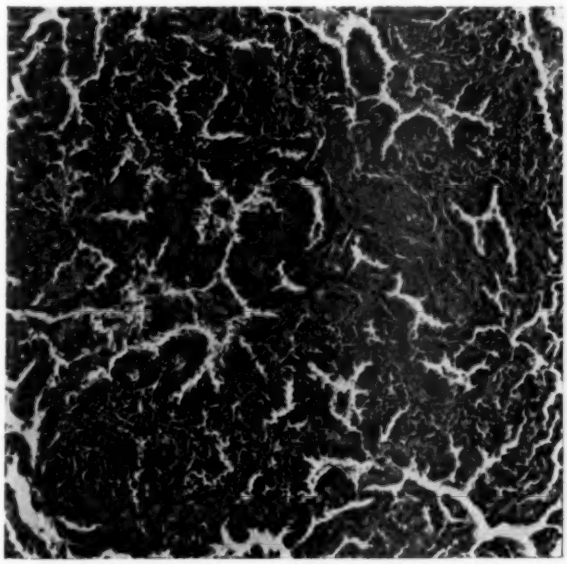

Fig. 9.—Focus of interstitial fibrosis with alveoli lined by epithelial-like cell. (Hematoxylin-eosin stain; ×75.)

The arterioles and precapillaries exhibited widespread changes varying from a slight fibrous broadening of the poorly nucleated wall to heavy obstructive proliferations of delicate connective tissue fibrils situated internal to the elastic membrane (Figs. 6 to 8). A mild increase in the number of endothelial nuclei was often present. In some instances, the lumen was obliterated by a patch of collagen. The adventitia usually showed fibrosis; this layer often stood out as a prominent cuff that was thicker than the rest of the wall. Changes in the septal capillaries were difficult to evaluate, but in eleven cases the basement membrane appeared accentuated, and diffuse homogeneity of the alveolar wall was sufficiently extensive to be considered of importance.

Foci with adenomatoid appearance were present in three cases (Fig. 9). Small oval septal cells lined the constricted alveoli, and the alveolar walls were thickened and infiltrated with lymphocytes. The lining of air spaces by septal cells was observed rarely in a more diffuse distribution, particularly near the pleura or fibrously thickened interlobular septa. In the specimen which showed the nodular arterial lesions, large patches of dense scar tissue obliterated many alveoli. Mild degrees of interstitial fibrosis were extensive in six other cases. Mild to moderate interstitial and bronchiolar infiltration with lymphocytes was occasionally seen.

Accumulation of iron pigment occurred in seventeen cases. Large numbers of heart-failure cells were pooled in the alveoli in nine cases. Lesser amounts of granular pigment in the interstitial tissue were revealed by the special stain. The presence of iron was regarded as the main indication of chronic passive congestion. In contrast, precipitated edema fluid was found in only one case.

Control Cases.—As we have observed similar vascular lesions in elderly patients, in certain cases of primary pulmonary hypertension, and in other unrelated diseases, four control groups of twenty-five cases each were selected from autopsy material for comparative study. One or more sections from the periphery of the lung in each case were utilized. The results are summarized in Table II. The muscular arteries and arterioles were considered together, and the predominant degree of vascular change, with reference only to the over-all thickening of the walls, was recorded. The customary vascular dilatation in autopsy specimens offered the main difficulty in making a valid comparison with the biopsies.

TABLE II. DEGREES OF PULMONARY VASCULAR CHANGE IN BIOPSIES COMPARED WITH FOUR CONTROL GROUPS OF 25 CASES EACH FROM AUTOPSY MATERIAL

GROUPS	AGE OF PATIENTS (YR.)	ARTERIAL LESIONS			
		ABSENT	MILD	MODERATE	SEVERE
Lung biopsies in mitral stenosis	19-49	2	4	15	4
Autopsy specimens in mitral stenosis	17-49	4	8	9	4
Normal young controls	21-43	15	9	1	0
Normal older controls	50-70	7	9	9	0
Older controls with ASHD or HHD and chronic passive congestion	50-70	3	12	10	0

As is seen from Table II, the severity of vascular alterations in the lungs of patients who died from rheumatic valvular disease was about the same as in the biopsy series. Edema, of both the parenchyma and the vessel wall, endothelial proliferation, and medial hypertrophy were more conspicuous features in several cases. Indeed, four of these patients showed vascular edema and much cellular proliferation reminiscent of the changes observed by Parker and Weiss.[2] Several cases also exhibited interstitial pneumonia. The control patients in the young age group, who were free from pre-existing lung or heart disease, with one exception, showed only mild changes at most. The patients from 50 to 70 years of age with arteriosclerotic or hypertensive heart disease and chronic passive congestion, but without primary lung disease, showed somewhat more advanced changes than those observed in the older patients who had no heart disease. The vascular alterations in both of the older age groups were, on the whole, less severe than those of rheumatic fever. Also in these older patients, the media were much thinner, and markedly fewer numbers of intramural nuclei were present. Intimal elastification was present, but was not as striking.

PHYSIOLOGIC OBSERVATIONS

The relationships of the mean pulmonary arterial pressure, pulmonary "capillary" pressure, cardiac index, pulmonary arteriolar resistance, the rise of pulmonary arteriolar resistance with exercise, the age of the patient, and the duration of symptoms were examined in the light of the degree of organic vascular change. A positive correlation appeared to exist between the structural changes and the pulmonary arteriolar resistance. Because the evaluation of the lesions did not permit mathematical values, a statistical correlation was not possible. The three biopsy specimens that showed the most extensive obstructive alterations were from the patients with the highest resting pulmonary arteriolar resistances. With one exception, all patients with pulmonary arteriolar resistances above 250 dynes sec./cm.$^{-5}$ exhibited moderate or severe organic changes. When the resistance was below this level, the trend was toward milder lesions although there was considerable variation in this group. The mean pulmonary arterial pressure and the changes in the pulmonary vasculature also tended to show a positive relationship. In all patients with a mean arterial pressure above 40 mm. Hg, severe or moderate lesions were present, whereas with pressures below 30 mm. Hg, the lesions were more often mild. The notable exception was one patient (Case 8), who had an elevated arterial pressure of 40 mm. Hg, and a resting pulmonary arteriolar resistance of 397 dynes sec./cm.$^{-5}$, but exhibited no vascular lesions.

Thus, in general, the increased thickness of the vessel walls and the decreased diameter of the lumina showed a correlation with the height of the pulmonary arteriolar resistance and the mean pulmonary arterial pressure.

DISCUSSION

The vascular lesions resembled those previously described in rheumatic heart disease.[1-6] Hypertrophy of the media has been emphasized as a major finding. Larrabee and associates[3] noted this feature in fifteen of their twenty cases. Henry[4] observed muscularization of arterioles and medial hypertrophy in 40 per cent of his cases. Enticknap[5] also stated that hypertrophy of the media dominated over hyaline changes. In our biopsy material, the incidence of medial hypertrophy was in substantial agreement with that of Henry[4] and Clowes and his associates.[6] Intimal alterations were more extensive than thickening of the media.

The determination of the lumen-to-wall ratio by Clowes and his associates[6] enabled them to conclude that no correlation was present between thep ulmonary arterial pressure or arteriolar resistance and the lumen-to-wall ratio; a significant correlation was found between the lumen-to-wall ratio and the product of the pulmonary arterial pressure times the duration of symptoms. We had not considered it necessary to determine the lumen-to-wall ratio, because the over-all appearance of the vessels in many fields was thought to provide a more satisfactory evaluation. This approach precluded statistical analysis. We were convinced, however, by the study of the controls, where vascular dilatation was the rule, that narrowed vessels might yet be capable of considerable distention. Small lung

specimens, which were obtained under abnormal physiologic conditions, were relatively bloodless, and were partially collapsed, did not lend themselves to mathematical interpretation. We are in agreement with Enticknap[5] that the level of the mean pulmonary arterial pressure does correlate with the vascular changes, although there were wide variations among individual cases.

The most commonly recognized factor that contributes to the development of vascular lesions in mitral stenosis is increased pulmonary arterial pressure. The slight-to-moderate elevation of this pressure in patients with mild or early mitral stenosis may be explained on the basis of transmission of back pressure from the left atrium and pulmonary venous system. This may be considered a passive elevation of the arterial pressure, dependent on the rise of the pulmonary venous pressure; the pressure gradient from the pulmonary artery to the pulmonary capillary bed is altered but little. As the gradient from the pulmonary artery to the pulmonary capillary bed increases, increased resistance on the arterial side of the capillary bed is indicated. Thus, a moderate to severe increase in arterial pressure can no longer be considered the direct result of mitral stenosis. Bayliss and associates[9] concluded that increased arteriolar resistance plays an important part in the development of severe pulmonary hypertension and that an increase in arteriolar tone probably precedes permanent structural changes. Lucas and Dotter[10] also stressed the functional as well as the organic aspect of the arteriolar resistance. The mechanism responsible for the development of vasoconstriction and active pulmonary arterial hypertension remains to be elucidated.

The degree of organic vascular obstruction in almost all of our cases did not appear to be of sufficient magnitude to account for the existing levels of pulmonary hypertension. Furthermore, the one patient (Case 8) with severely altered hemodynamics exhibited no vascular lesions. This finding corroborated the opinion that organic changes do not necessarily precede the development of hypertension. Imbalance of the autonomic nervous system is a possible cause of the pulmonary vasoconstriction. A reflex relationship may exist between distention of the pulmonary veins due to valvular stenosis and arterial constriction.

Baker and his associates[11] reported two patients with severe pulmonary hypertension in whom a dramatic decrease in the level of the pulmonary artery pressure occurred six months after mitral commissurotomy. In one patient the pulmonary artery pressure decreased from 130/56 mm. Hg to 40/10 mm. Hg within this period. The lowering of the pulmonary venous pressure following surgical relief of the obstruction of the mitral valve may in some unexplained manner affect the autonomic imbalance, with resulting abolishment of reflex vasoconstriction.

Carbon dioxide and oxygen tension values within the alveoli and pulmonary arteries may affect the tone of the vasculature. However, studies in this laboratory would suggest that alteration in the gaseous tension is not of prime importance in the resting state. The decrease in oxygen tension of the pulmonary arterial blood, which occurs with exercise, is considered to contribute to further increases in the pulmonary arterial pressure.

The occurrence of similar arterial changes in older nonrheumatic patients might indicate that age is a significant factor in the production of lesions.[12] It is of interest that Karsner and Bayless[13] employed the concept of precocious aging in their discussion of the sclerosis of the coronary arterial tree in rheumatic fever. As the pulmonary vascular changes in older age are somewhat different especially in regard to the absence of medial hypertrophy, are usually less severe, and are unaccompanied by pulmonary hypertension, the age factor should be minimized. Table I shows that several patients above 40 years of age with symptoms of long duration had less severe lesions than younger ones, and this was also true in the control series. Parker and Weiss[2] commented that their patients who had milder alterations were of more advanced age.

Because age and elevated arterial pressure do not fully explain the pathogenesis of the lesions, the role of rheumatic fever itself should be considered. The presence of focal pulmonary adenomatosis, inflammatory and necrotizing vascular lesions,[2,5] and diffuse interstitial inflammatory reactions point to that possibility. Admittedly, the vascular changes are nonspecific, but a situation may exist in the lung similar to that in the brain where fairly distinctive rheumatic lesions have been described.[14] Conceivably, the inflammatory lesions in the myocardium and endocardium of the atrial appendages, apart from the Aschoff nodule, are analogous. Regardless of the nature of the agent that injures the blood vessel, the variety of reactions is limited. The severity of rheumatic endocardial lesions shows little relationship to the age of the patient or to length of illness; the same appears to be true of the severity of the pulmonary vascular lesions.

A tentative conclusion may be drawn regarding the significance of the vascular lesions in the postoperative course of the patient. McGregor and his associates[15] stated that pulmonary hypertension may persist for months after commissurotomy. Welch and associates[16] reported a fatal case of mitral stenosis in which obstruction of the pulmonary circulation did not appear to be relieved by commissurotomy. Larrabee and associates[3] thought that those patients with intimal or medial fibrosis would not benefit from surgery, but that others with only medial hypertrophy would obtain relief. We favor the view of Clowes and his associates[6] that the presence of pulmonary vascular lesions does not contraindicate surgery. Vascular obstruction in almost all of our cases did not appear extensive enough to bar clinical improvement. It is conceivable, however, that in a significant percentage of cases, the flexibility and distensibility of the small vessels might be sufficiently reduced to cause a moderate pulmonary hypertension on exercise. The presence of coexisting valvular lesions and the severity of the rheumatic involvement of the myocardium are probably of greater importance than the pulmonary vascular alterations in predetermining the extent of improvement that follows surgical relief of the obstruction of the mitral valve. Until physiopathologic studies are made on a group of these patients after the lapse of one year or more following surgery, the questions of "irreversibility" of the lesions and the possible prognostic value of lung biopsy will not be answered.

ATRIAL APPENDAGES

The lesions in the left atrial appendage removed at the time of operation for mitral stenosis were discussed at the meeting of the American Association of Pathologists and Bacteriologists in April, 1953. This essay was based upon s survey of fifty patients. The number of cases has increased to seventy-five in the meantime. The results are summarized here since a number of articles on that subject have appeared recently.

Endocardial and epicardial fibrosis with or without occasional lymphocytic infiltration occurrred almost constantly, but it should be kept in mind that the endocardium of the left atrium and its appendage under normal conditions is much thicker than that of the other chambers.[17] Hypertrophy of the myocardial wall, usually mild to moderate, but occasionally more severe with thickness up to 5 or 6 mm., was present in nearly every case. Thrombi were found in 36 per cent, rheumatic carditis (both endocarditis and myocarditis) with Aschoff bodies in 28 per cent; chronic nonspecific myocarditis in an additional 28 per cent, and myocardial fibrosis in 12 per cent of the cases. Thrombosis and Aschoff bodies appeared to exclude each other to a certain extent. There was only one case with both features. A similar observation has been made by others, notably Decker and his associates.[18] The incidence of Aschoff bodies declined with advancing age, a fact mentioned recently by McNeely and associates[19]; the average age of our patients with Aschoff bodies was 33 and that of those without Aschoff bodies, 39 years.

The frequency of thrombotic material in the left atrial appendage, recently discussed by Wallach and his associates,[20] which is so often the source of emboli to other organs, especially the brain, appeared to justify the removal of that part of the heart. According to Jordan and associates[21] thrombi are confined to the atrial appendage in nearly 50 per cent of the cases.

The presence of inflammatory lesions was in striking contrast to the fact that in our experience chronic rheumatic patients often exhibit little or no change in other sites of the myocardium. However, Kuschner and Levieff,[22] on the basis of studies of autopsy material, stated that "rheumatic activity" in the appendage ". . . would seem to indicate that lesions are very likely to be present elsewhere in the heart." There was no clear-cut correlation in our cases between "rheumatic activity" and elevated sedimentation rates, a fact recently emphasized by McNeely and associates.[19] Karsner[23] has pointed out in a critical review of several pertinent papers that ". . . it would appear that at the present moment it is, practically speaking, impossible to determine in advance that rheumatic fever is active."

The presence of Aschoff bodies in the left atrial appendage does not presage an unfavorable development in the postoperative condition of the patient. Follow-up study of the cases with Aschoff bodies indicated that in at least one-half of the patients, the results of the operation were good to excellent. A thorough evaluation of the clinical results is beyond the scope of this study, and obviously would not be reliable until a postoperative period of several years had elasped.

Such evaluation must include the possibility of reactivation of the rheumatic fever following surgery, described recently by Soloff and his associates.[24]

Our results are in general agreement with those published by others since 1952.[25-30]

SUMMARY

Lung biopsies from twenty-three patients with mitral stenosis who were studied by cardiac catheterization prior to mitral commissurotomy were examined histologically. In the majority of cases the muscular arteries and arterioles exhibited prominent fibroelastic intimal thickening, and in 32 per cent the media appeared hypertrophic. In general, a positive correlation existed between the degree of vascular alteration and the pulmonary arteriolar resistance and mean pulmonary arterial pressure in the more severe cases of pulmonary hypertension. The hemodynamic pattern varied considerably in patients who exhibited less severe vascular lesions. A functional component was believed to be of as great importance in the development and maintenance of pulmonary hypertension as the organic vascular changes. It was considered that surgery should not be denied the patient either on the basis of data obtained by cardiac catheterization or because of the pulmonary vascular lesions, which are not usually severely obstructive although almost always present.

The histologic findings in seventy-five resected atrial appendages were reviewed; the results were in general agreement with those of other recent investigations.

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THE DYNAMICS OF MITRAL INSUFFICIENCY

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IN mitral regurgitation the left-ventricular contents can flow either forward into the aorta or backward into the left atrium. Reflux through the mitral valve begins during early isometric contraction before the opening of the aortic valves and continues throughout the period of aortic ejection. However, forward output into the aorta cannot take place until the intraventricular pressure is higher than the aortic pressure. The greater facility of regurgitation in mitral insufficiency has repeatedly posed a dynamic problem which has remained relatively ignored, and only partially answered: the problem as to what prevents the entire ventricular contents from being regurgitated, leaving nothing for forward flow.

The importance of the problem does not depend only upon the situation at the mitral valve. The special dynamics of the divided flow in mitral insufficiency can probably be applied generally to other situations in which two outlets with differing resistances are present. This includes situations such as tricuspid insufficiency and the defects between the ventricles or between the great vessels.

The recent development of surgical approaches to the therapy of mitral valvular disease has emphasized the need for further elucidation of these hydrodynamic problems. For these reasons an attempt has been made to provide a basis for understanding the dynamics of flow under these conditions, by approaching the problem of mitral regurgitation analytically on the basis of hydrodynamic principles.

HISTORICAL REVIEW

Partial answers have been given to the special problems of divided flow in mitral insufficiency using a variety of approaches. These include mathematical analysis of the cardiodynamic events, clinical observations and study, experiments on animals, and resort to artificial circulation schemata. Prior to 1890, von Basch[1] had designed circulation models and used them to assay the hydrodynamic effects of various valvular lesions. Moritz[2] also utilized an elaborate schema to study cardiovascular dynamics. He concluded that mitral regurgitation causes a systolic pulsatile expansion of the left atrium with a rise in its pressure, which in turn would increase left ventricular filling during the succeeding diastole. The forward cardiac output would thereby be restored toward normal at the expense of a heightened stroke output. Moritz further suggested that a gradual expansion of the blood volume would eventually follow. When marked, the heightened left atrial pressure would be transferred to the lesser circulation, and pulmonary arterial hypertension would ensue.

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Aided by the National Heart Institute (H-690).

Received for publication April 25, 1954.

Schwarz* in 1905[3] attacked the problem mathematically and suggested that mitral regurgitation occurred primarily during early systole. He reasoned that progressive dilation of the heart would increase the energy released by the ventricles and thus compensate for the energy loss due to the incompetent valve.

MacCallum and McClure[4] produced acute mitral insufficiency by sectioning the chordae tendineae in dogs. They observed an acute fall in systemic blood pressure with marked fluctuations of the left atrial pressure during the heart cycle. However, the pulmonary arterial and systemic venous pressures remained unchanged. No attempt was made to measure the actual degree of regurgitation. Calculations showed that if the per cent of regurgitation remained constant, an increasing left atrial pressure and ventricular filling would result in a heightened forward flow, thereby tending to compensate for the insufficiency. McDowall[5] also found the left atrial pressure to be increased in experimental mitral insufficiency without an increase in pulmonary arterial or systemic venous pressure.

Straub[6] mechanically prevented closure of the mitral valve in dogs and concluded that ventricular dilation was the important compensatory mechanism. His stromuhr records show a significant transient fall in forward cardiac output with a rapid return to control levels. This clearly demonstrated that physiologic adjustments could compensate, at least in part, for the mitral reflux.

On the basis of optical pressure recordings in dogs, Wiggers and Feil[7] concluded that regurgitation occurred during the entire period of systole including isometric contraction and ejection, as well as during protodiastole. Increased ventricular filling was considered to be important in the adjustment to the insufficiency. A rise in systemic arterial pressure was considered to increase the tendency to regurgitation, since constriction of the aorta increased the amplitude of the atrial pulsations and the atrial pressure level.[7] The duration of the phases of systole in patients with clinically diagnosed mitral insufficiency was similar to the duration in normal subjects.[8]

The foregoing studies and others[9-14] have provided a basis for the understanding of the mechanism of compensation for mitral insufficiency. Some of the special problems in divided flow in rigid pipes have been treated mathematically by hydraulic engineers,[15] but these cannot be applied conveniently to the special problems posed in the present study.

METHODS

Specially designed circulation models were utilized in an attempt to analyze and quantify some of the factors contributing to the tendency to regurgitation. The basic model (Fig. 1) consisted essentially of a balloon-like "ventricle" (*V*) which filled by gravity from a reservoir during diastole. The ventricle consisted of either an inelastic parchment bag of dried sheep cecum, or of a latex rubber condom. These represented two extremes to the approach to the properties of the heart. Both were found useful in the present study. The parchment was used in studies requiring a constant end-diastolic volume. Latex was used to permit varying degrees of filling depending on atrial pressure or on duration of diastole.

Details of the air-pressure distributor-valve mechanism producing ventricular contraction have already been described.[16] At the onset of systole, compressed air enters the glass chamber (*C*) enclosing the ventricle, thereby causing ventricular contraction. Needle valves control the flow of compressed air, permitting control of the celerity and strength of contraction. During ventricular systole the ball valve between the filling reservoir and the ventricle closed; the ejected blood could then pass either through the "mitral" valve (*M*) into the atrium, or through the "aortic" valve (*A*) into the aortic chamber. This design

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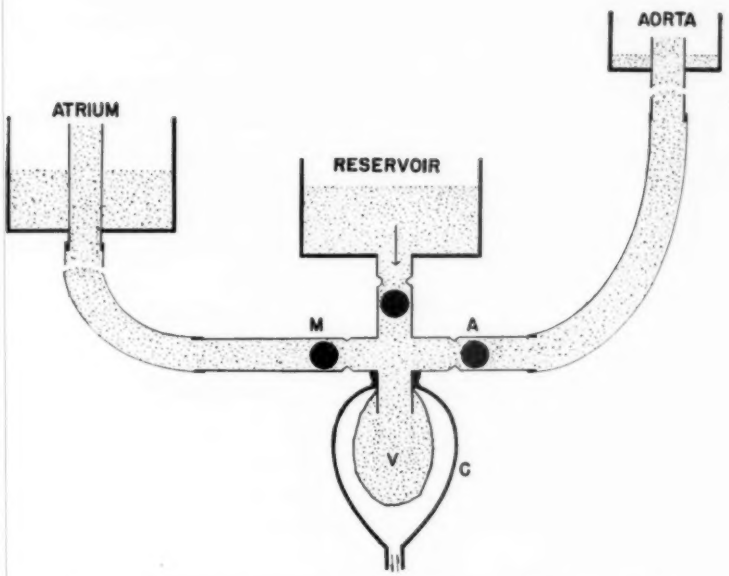

Fig. 1.—Principle of artificial circulation model. Described in text.

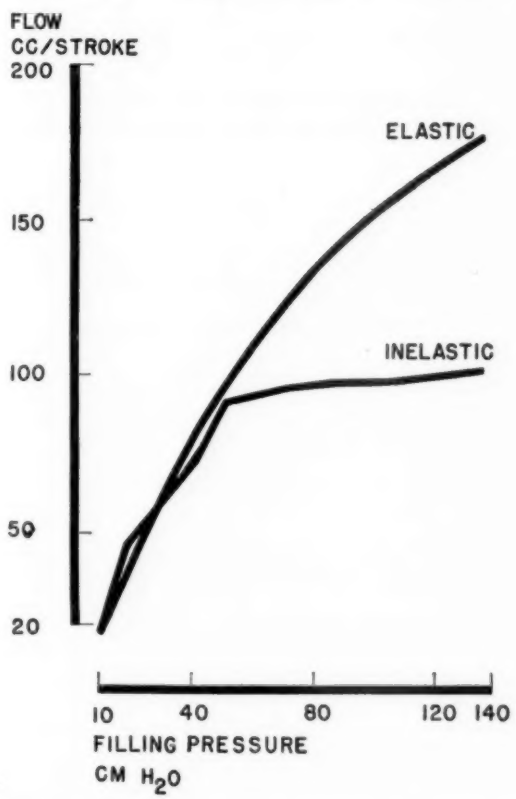

Fig. 2.—Relationship between ventricular filling pressure and stroke output. Pulse rate was constant throughout. Filling of the elastic and inelastic ventricles (so labeled) was equal up until the limit of filling of the latter. Discussed in text.

effectively separated the "filling" from the "regurgitant" volumes of the atrium. The compressed-air valves providing energy for ventricular contraction were adjusted to accomplish complete emptying of the ventricle in each beat.[16] Unless otherwise noted, the heart rate was kept constant at ten per minute. The volume of fluid passing into either the atrial or the aortic chambers was determined after a specified number of contractions.*

RESULTS

A. With a Competent Mitral Valve.—Control experiments, to serve for comparison, were performed by closing the regurgitation orifice with a pinch clamp. Under these circumstances, the entire ventricular volume was pumped forward through the aortic valve into the aortic collecting chamber.

The height of the arterial pressure in this arrangement, as expected, had no effect on the volume output. When a parchment ventricle with a fixed end-diastolic volume was used, the filling also had no effect on the ventricular output, provided the ventricle filled completely during each diastole. When a latex ventricle was used, an increase in filling pressure resulted in an augmented ventricular filling and a consequently increased cardiac output. Since the resistance to filling of the rubber ventricle was slight, the output was closely proportional to the filling pressure (Fig. 2).

B. Analysis of Some Factors Involved When the Mitral Valve is Incompetent.—When the orifice between the ventricle and the regurgitation chamber was opened, the ventricular output was divided between the two possible avenues: "aortic" and "atrial." The proportions entering each depended on the setting of several factors.

The intrinsic resistance of the apparatus was tested by setting the atrial and aortic reservoirs at the same level. Under these circumstances one-half the ventricular output passed into the aorta, and one-half regurgitated into the atrium. These results showed that the inherent resistances due to the dimensions of the tubings in the two outflow tracts were nearly equal. Any differences in outflow must therefore depend on imposed changes in the system.

The following sections describe the results obtained by keeping all factors constant except the one under analysis. Unless otherwise noted, the parchment ventricle (constant end-diastolic volume) was used. The experiments in sections 1 and 2 were carried out with aortic and mitral orifices of 50 square millimeters each.

1. Arterial pressure head: In the presence of an incompetent mitral valve, the level of the arterial pressure head had a marked effect on forward flow (Fig. 3). As noted above, ventricular outflow was divided equally between atrium and aorta when the pressures in the two outflow tracts were equal. When the

*The resistances to outflow which were used in the present study consisted of columns of fluid set at a predetermined height. It was found that this standpipe type of resistance gave consistent results which were amenable to simple analysis. The standpipe system simulates the conditions prevailing in the ventricle-outflow tract system since the heart must pump against a pressure head. Some arrangements which have been used in the past have utilized flow resistances which operate on the basis of Poiseuille's law; these resistances vary with the volume flow, simulating conditions which hold in flow through small vessels but not with the energetics of ejection.

arterial pressure was raised 25 cm. of water above the atrial pressure, forward flow was reduced to 36 per cent of the total output. Further increases in the arterial pressure resulted in a progressive linear reduction in the aortic flow. At an arterial pressure 85 cm. of water above atrial pressure the forward flow was only 20 per cent of the ventricular output.

The profound effect on forward output of the arterial pressure head is thus demonstrated. If an adequate forward flow is to be provided by ventricular activity, other factors must operate to enhance it. Among these are the effect of atrial pressure and the role of orifice size.

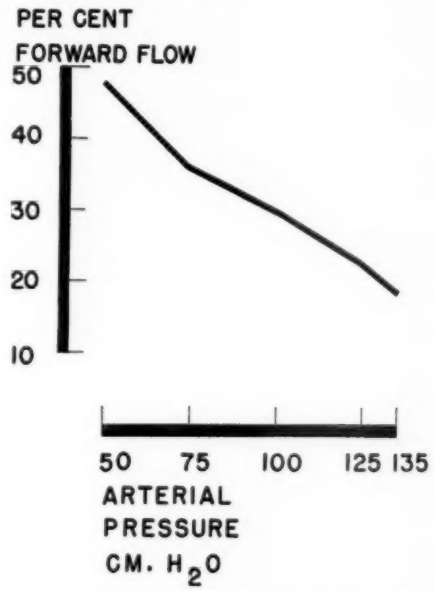

Fig. 3.—Effect of increases in arterial pressure on forward flow. Atrial pressure was set at 50 cm. water. When atrial pressure was at the same level as the arterial pressure the division between the potential pathways was equal. An increase in arterial pressure reduced the forward flow. Discussed in text.

2. *Atrial pressure*: An increase in atrial pressure was shown to enhance forward flow by two discrete mechanisms. Increments in atrial pressure exactly balanced the effect of equivalent pressure rises in the aorta. Thus, a rise in atrial pressure of 20 or 40 cm. water had the same effect on forward flow as a fall of like amounts in arterial pressure. The effects of a rising atrial pressure can therefore be computed from Fig. 3. by subtracting the atrial pressure from the abscissal value. Rising atrial pressure thus may compensate for mitral regurgitation in an amount equal to its pressure head. The effective resistance to forward flow is thus seen as the difference between the aortic and atrial pressures.

An increase in atrial pressure also acts on end-diastolic ventricular volume. To analyze this effect the latex rubber ventricle was used. A rise in filling pressure in this experiment resulted in an increased ventricular filling (Fig. 2). The per cent of fluid regurgitated remained essentially unchanged, leading in turn to a larger volume of fluid being pumped forward into the aorta. In the important terms of forward flow, it must be considered that the effectiveness

of the ventricle in the face of mitral regurgitation was increased in step with the increased ventricular end-diastolic volume (Fig. 2), since the aortic output increased pari passu with the increated ventricular output.

End-diastolic ventricular volume may increase not only as a result of a raised atrial pressure, but also when diastole is prolonged, or when the capacity of the ventricle to stretch is increased (equivalent to a decrease in tone). No differences in the division of the stroke output could be demonstrated among these three mechanisms.

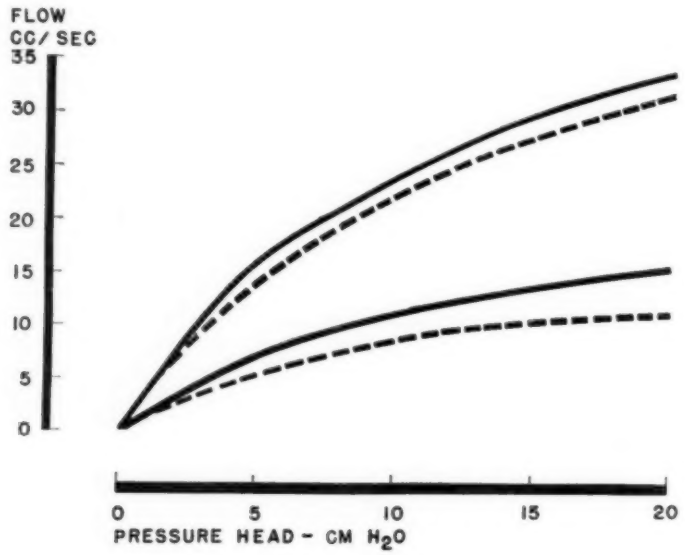

Fig. 4.—Flow through orifices of two different areas. The driving head is given on the horizontal axis; the volume flow is given on the vertical axis. The unbroken lines give the flow curve for each orifice flowing separately, with that for the larger being above. The two broken lines give flows through each of the orifices when both were open simultaneously. Discussed in text.

3. Flow through one orifice: An important factor limiting regurgitation is the nature of the regurgitant orifice. Ideal flow through orifices is known to depend primarily on the effective driving pressure and the orifice area.[17] Volume delivered is proportional to the square root of the effective pressure head, being limited by the area of the orifice through which it must pass.*

The flow through the several orifices utilized in the current experiments was measured under different heads of pressure, and flow curves were obtained which fitted well with the equation given above (Fig. 4). The contraction factor for the large circular orifice (20 mm.^{2} area) was found to be 0.46; the value for the small circular orifice (7 mm.^{2} area) was 0.57.

*The relationship is expressed by $Q = A\sqrt{2gP}$ in which Q is the quantity of flow, A is the orifice area, g is the gravity constant, and P is the effective pressure head.

In practice it has been shown that during flow through an orifice the stream lines arrange themselves so that the effective opening is somewhat smaller than the actual diameter. The actual orifice area is therefore corrected by a contraction factor, C, which is less than unity. The numerical value of this contraction factor must usually be obtained empirically since it may vary markedly, depending on the shape, length, and orientation of the orifice with respect to the stream. The relationship thus becomes $Q = C A\sqrt{2gP}$; quantity of flow equals the orifice area multiplied by the contraction factor and by the square root of the effective pressure head.

4. Orifice competition: The volume flow through two or more orifices in a single chamber is not affected if these openings are at sufficiently great distances from each other (Fig. 5, *A*). This is due to the fact that in such a case the streamlines entering one orifice are distinct from those entering the distant orifices. In mitral insufficiency two orifices, the mitral and the aortic, lie side by side, and they may be considered as competing for the available streamlines of flow. This relationship would necessarily markedly affect the flow patterns described by the formulas given previously. Experiments were therefore undertaken to determine the effect of an adjacent orifice on flow.

It appeared advantageous for these studies to have an atrial orifice smaller than the aortic orifice. In this fashion it was possible to maintain some forward flow when adverse factors were introduced. For this reason the small (7 mm.^{2}) orifice was arbitrarily selected for the mitral regurgitant opening, and the large (20 mm.^{2}) orifice was used for the aortic opening.

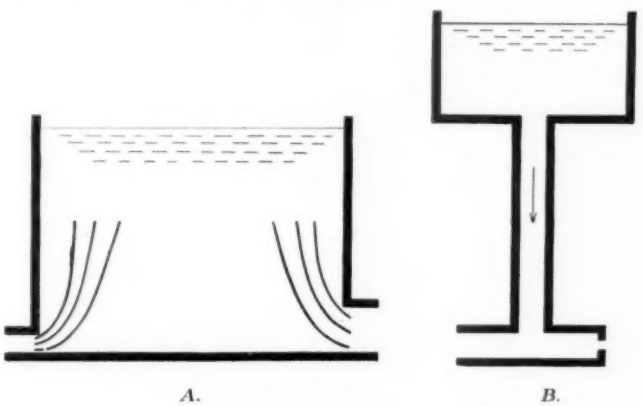

Fig. 5.—Orifice competition. Diagram *A* shows a large tank with two orifices at a great distance from each other. The streamlines feeding one orifice do not impinge significantly on those feeding the other orifice. Diagram *B* shows schema to study the effect of adjacent orifices. The tank supplies fluid which may flow through either the left or right orifice. The two orifices may be considered as competing for the stream lines. Discussed in text.

A column of water maintained at 150 cm. was used to drive fluid through a length of rubber tubing of 12 mm. diameter (113 mm.^{2} in cross-section area) according to the schema in Fig. 5, *B*. The effluent was collected after passing through either a single orifice or through the two competing orifices. The results obtained made it clear that the simple hydraulic formula for a single orifice could not be applied directly in the case of orifice competition. Actually, the effect of competition was to reduce the flow through both orifices. The effect of this competition was more marked on the small orifice than on the adjacent larger one. Thus, the flow through the large orifice was reduced to 92 per cent of its original value, while the flow through the small orifice was reduced to 70 per cent of its original value.

The mechanism operative in the competition of orifices depends upon the streamline effects due to laminar flow. When a column of water stands above an orifice, gravitational pull causes flow through the opening. An adjacent orifice likewise provides a pathway of fall for the column directly above it. The stream-

lines perpendicular to the wall between the two orifices are now divided between them on the basis of the rate of flow through each. Flow through the larger orifice is thereby affected to a lesser extent than is the flow through the smaller orifice.* This new balance of flow is not expressed by the orifice formulas given here. A new correction factor must therefore be used to express accurately the state of affairs in the case of competing orifices. In the present study the new correction factors were found to be 0.43 for the large orifice and 0.44 for the small orifice.

In the heart the sizes of the orifices available for outflow are subjected to various influences. For example, the aortic orifice is probably stretched to a small extent by a rise in aortic pressure. Much more significant for our present analysis, however, is the effect of intraventricular pressure changes on the mitral regurgitant orifice.

5. Lateral pressure effects on orifice area: With the onset of myocardial contraction and the rise of intraventricular tension, the lateral pressures exerted on the ventricular surfaces of the mitral valves cause the leaflets to approach each other and thereby reduce the potential regurgitation area. This is a direct effect equivalent to the instantaneous pressure, multiplied by the surface area on which it acts. The large surface area of the mitral valve provides a considerable force enhancing this tendency to closure, thereby reducing the tendency to regurgitation.

Studies were undertaken to determine the effect of such a force on an elastic orifice. The model used was based on that shown in Fig. 5, *B*. The smaller orifice was replaced with a segment of soft rubber Penrose tubing (6 mm. diameter, 4 cm. long), which served as a "valve." The Penrose tubing was enclosed in a glass cylinder† so that various degrees of closing pressure could be applied against the outer (ventricular) walls of the "valve." A driving head (intraventricular) of 150 cm. water was used throughout. When no pressure was applied to the outer walls of the Penrose segment, a flow of 47 ml./sec. was obtained (Fig. 6, *A*). Incremental increases in the pressure acting to push the walls of the "valve" together produced a progressive reduction in flow (Fig. 6, *A*). At a closing pressure of 140 to 150 cm. water, a seepage flow of less than 5 ml./sec. was observed.

For the same pressure head, 40 ml./sec. passed through the fixed aortic orifice (Fig. 6, *B*) when this was the sole route of flow.

When flow was permitted simultaneously through both the aortic orifice and the elastic "valve," the volumes delivered through each were markedly affected; in the case where no closing pressure was applied to the mitral valve the delivery through the elastic "valve" fell from 47 to 34 ml./sec. (Fig. 6, *C*). This effect became more notable as the closing pressure acting on the valve was raised. At a closing pressure of 100 cm. water, 7 ml./sec. was delivered (compare with 22 ml./sec. when no aortic competition was present). The seepage flow at closing

*The physical effect is probably due primarily to changes in the effective pressure heads operating at each orifice. However, it is not easy to determine this effect directly. Calculations suggest that in the case of competing orifices, the contraction factors for both tend to approach a common value.

†This type of apparatus has been used for many years as a "resistance" to flow in the Starling heart-lung preparation, and is often referred to as a Starling resistance.

pressure of 150 cm. water was only one-half that obtained when no aortic orifice was in competition (Fig. 6, *C*).

Flow through the rigid aortic orifice (Fig. 6, *D*) was only 29 ml./sec. when the elastic mitral "valve" was freely opened (compared with 40 ml./sec. when only aortic flow took place, Fig. 6, *B*). Increases in the mitral closing pressure with its reduced mitral flow were accompanied by a rise in the aortic outflow. This approached the value obtained when the mitral valve was completely obstructed.

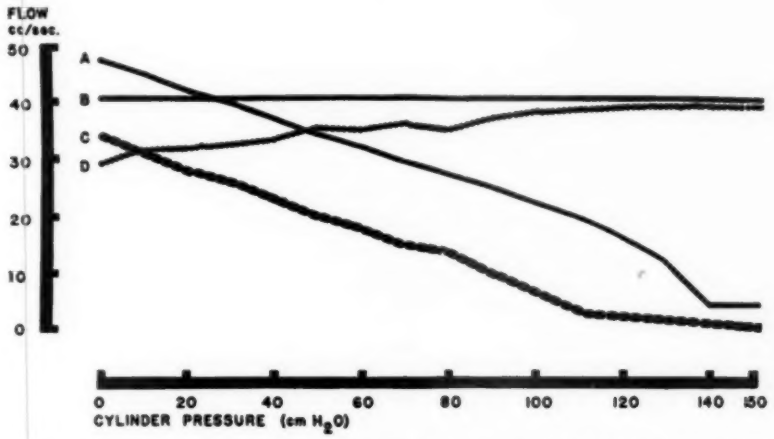

Fig. 6.—Distribution of flow between a fixed aortic orifice and a "collapsible" mitral orifice. Driving pressure was kept constant at 150 cm. water. Lines *A* and *B* show flow through each orifice when the other is completely obstructed. Line *A* gives the flow (vertical axis) through a segment of elastic tubing as progressive increments of closing pressure are applied to its outer wall, simulating closure of the mitral valve. When the mitral orifice was completely closed off, flow through the single aortic opening was constant at 40 ml. per second (Line *B*). Lines *C* and *D* give the outflow when both the mitral and aortic orifices were simultaneously open. It can be seen that the outflow through the collapsible (mitral) opening (Line *C*) was significantly reduced when flow was permitted through the aortic opening. As the closing pressure was raised, thereby reducing the size of the orifice, this effect became marked. At a cylinder pressure of 100 cm. water (surrounding the mitral valve), for example, the outflow through the single mitral orifice was 22 ml. per second while in the presence of the open aortic orifice the mitral flow was only 7 ml./sec. The aortic flow was enhanced (Line *D*) as the cylinder pressure acting on the mitral valve was raised. The net effect of progressive closure of the mitral valve was to increase the efficacy of forward delivery to a much greater extent than might have been expected by the application of single orifice formulas.

Considered from the point of view of forward delivery through the aortic orifice, the progressive closure of the mitral valve caused a marked rise in the efficiency of forward (aortic) delivery. When the mitral valve was completely open the forward delivery was less than 50 per cent of the total outflow (total equals *C* plus *D*, Fig. 6). The marked fall of Curve *C* with the rise of Curve *D*, as the cylinder pressure was raised, illustrated this effect.*

*When flow occurs through a soft-walled tube, the phenomenon of recurrent collapsibility (flitter) may be seen. The interchange of energy between lateral pressure and velocity produces an intermittent opening and closing of the tube with the production of vibrations and of a marked energy loss. (Rodbard, S., and Saiki, H.: Flow Through Collapsible Tubes, Am. Heart J. **46**:715, 1953.) This phenomenon very likely contributed to the increased resistance through the elastic segment utilized as a valve in our experiments. Direct observations of the diameter of an orifice have clearly demonstrated that the lumen is greater when there is no flow than when flow is permitted. Thus, the occurrence of flow itself operates to reduce the area of a collapsible vessel such as an artery or a vein (Rodbard, S., and Jannotta, F.: An Analysis of Oscillometric Pulsations, Circulation **7**:922, 1953). These data may be applied to valves, which may be considered to be collapsible tubes of very short length.

6. Pipe competition: In order to determine the effects of the differing atrial and aortic pressure heads on flow through two adjacent orifices, the model shown in Fig. 5,*B* was modified by attaching a tube to each of the outlets. Flow was thereby reduced in accordance with the height of the outlet from each orifice (Fig. 7). The atrial column was set at 10 cm. water, and the arterial column at 75 cm. The height of the source ("intraventricular" pressure) was varied from 25 to 150 cm. water. It was observed that such an arrangement strongly favored

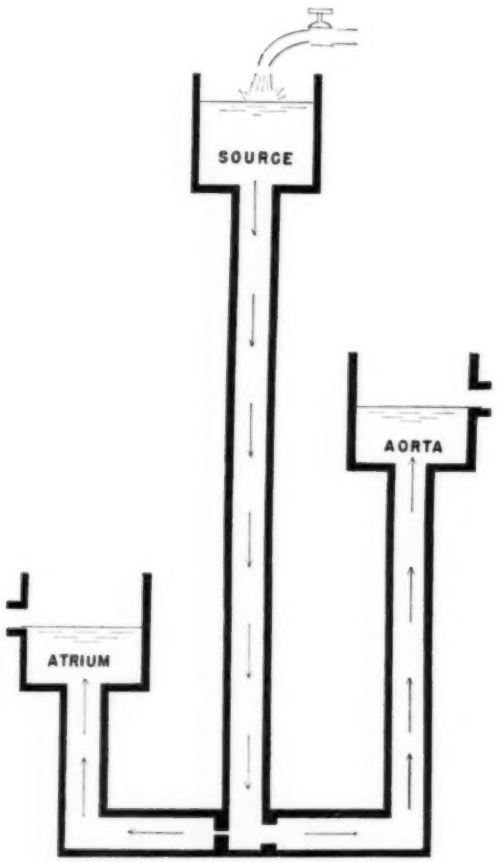

Fig. 7.—Pipe competition. Flow from the reservoir passes through the two competing orifices. The pressure heads beyond each orifice can be adjusted so that the effects of the differing aortic and atrial pressures can be compared. Discussed in text.

delivery in the mitral direction when both orifices were of equal size. Data given in Fig. 8 represent conditions when the mitral orifice was markedly smaller than the aortic orifice.

These data illustrated the fact that regurgitant flow begins as soon as the ventricular pressure (reservoir height) rises above the atrial level. The regurgitation, as expected, is a function of the square root of the driving pressure and is limited by the resistance due to the atrial orifice. With such an arrangement, flow into the aortic system does not begin until the intraventricular pressure

(reservoir height) rises above the aortic level. When the aortic valve is widely open, the resistance to forward flow is negligible. At low intraventricular pressures the predominant effect of the pressures beyond the orifices is to produce a marked preponderance of flow through the mitral orifice. At high ventricular pressures, the percentage of forward flow is enhanced.

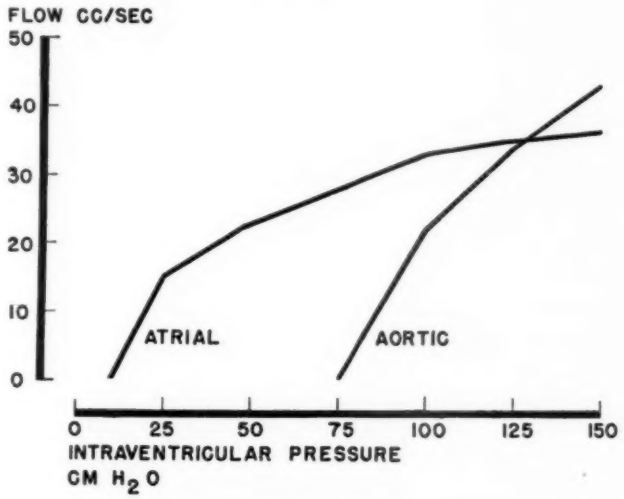

Fig. 8.—Relationship between intraventricular pressure and flow patterns in mitral insufficiency with constant atrial and arterial pressure heads, using the apparatus in Fig. 7. It can be seen that as the intraventricular pressure rises (horizontal axis), regurgitant (atrial) flow begins early and increases rapidly. When intraventricular pressure is at a level equal to the aortic pressure (75 cm. water), flow out of the *aortic* orifice begins. When flow takes place through both orifices, the effect of orifice competition is such as to enhance forward flow through the larger orifice as against regurgitant flow through the smaller (mitral) orifice. The diagram may be considered as points moving rapidly to the right as ventricular contraction takes place. Since some regurgitation occurs during the period before opening of the aortic valves, the interval should properly be called "isometroid" contraction phase. The larger aortic orifice results in a rapidly rising forward flow, but regurgitation continues throughout the forward ejection period. With the end of systole the points move rapidly to the left. The short duration of the "isometroid" phase permits a significant forward output.

Under any circumstances the mitral regurgitant orifice must be small if the heart is to function well. The efficient action of an intermittent pump is therefore seen to depend upon a rapid ascent in ventricular pressure, thereby reducing the duration of the period in which only regurgitation takes place. An approach to the dynamics of a pumping ventricle, as contrasted to the continuous flow models described here, was therefore undertaken.

7. Pulsatile flow effects: Experiments were designed to utilize the double orifice arrangement described here, with a pulsating pressure head produced by the model in Fig. 1. In these experiments the aortic pressure head was kept constant at 85 cm. water above the atrial level. When both orifices were of the same size (50 $mm.^2$), 75 per cent of the stroke output was regurgitated. Substitution of an atrial orifice of 20 $mm.^2$ had no notable effect on the regurgitation, which was than 73 per cent. However, reduction of the atrial orifice to 7 $mm.^2$ was accompanied by a reduction in the degree of regurgitation to 55 per cent.

These results illustrated the great importance of atrial orifice size in the tendency to regurgitation, since even small degrees of valvular insufficiency as measured by orifice area, can give rise to severe reductions in the ability of the mechanical heart to propel blood forward. The celerity of ventricular contraction could be expected to play a significant role in affecting the degree of regurgitation. Analysis of the effect of various durations of ventricular contractions was therefore undertaken.

8. Celerity of ventricular contraction: Experiments were carried out on the model in Fig. 1. The total duration of systole was set at 2.5, 1.0, or 0.5 second while keeping stroke output constant. This was accomplished by varying the rate at which air pressure entered the glass bulb surrounding the ventricle (Fig. 1.) The difference between the atrial pressure and the aortic pressure was maintained at 85 cm. of water.

When the area of the regurgitant orifice was equal to that of the aortic orifice, an increase in the celerity of ventricular contraction from 2.5 to 0.5 second resulted in the per cent of regurgitation falling from 90 to 73 per cent. Similar beneficial effects were demonstrated for the small orifices (Table I). These results showed that the celerity of pumping of the fluid out of the ventricle could significantly affect the efficiency of the pump in the maintenance of forward flow.

TABLE I. EFFECT OF CELERITY OF VENTRICULAR CONTRACTION ON PERCENTAGE OF VENTRICULAR OUTPUT REGURGITATED THROUGH ATRIAL ORIFICE*

DURATION OF SYSTOLE (SEC.)	ATRIAL ORIFICE SIZE		
	50 MM.²	20 MM.²	7 MM.²
	REGURG. %	REGURG. %	REGURG. %
2.5	90	87	64
1.0	77	72	55
0.5	73	68	52

*Aortic orifice size, 50 mm.²; aortic pressure, 85 cm. water above atrial level.

The effects produced by rapid contraction of the ventricle depend on the resistance to deformation of the ventricular contents, as they are extruded through the available orifices. Resistance to deformation due to the viscosity or plasticity of the blood therefore contributes to the distribution of outflow through the openings of the chamber. To assay these effects, studies on the effect of viscosity were undertaken.

9. Viscosity: An increase in the viscosity or plasticity of a fluid leads to a reduction in volume delivered for a given pressure head. Thus, for a given orifice of 7 mm.² and a pressure head of 20 cm. of water, 11 c.c. of water was delivered, while only 7 c.c. of cottonseed oil (viscosity, 70 times that of water) was delivered per minute.

The possibility that viscosity effects might play a significant role in valvular regurgitation was investigated. Sucrose solutions, 30 per cent, and 60 per cent, with viscosities 3 and 47 times that of water, respectively, were circulated through the model described above (Fig. 1). An increase in viscosity produced a small but significant improvement in the efficacy of the ventricle, measured in terms of per cent of forward flow (cf. Table II). For example, in a given experiment 13 per cent of the ventricular fluid moved out through the aortic orifice when water was used, while 22 per cent moved forward when it had a viscosity 47 times that of water (Table II).

TABLE II. EFFECT OF VISCOSITY ON PERCENTAGE OF VENTRICULAR OUTPUT REGURGITATED THROUGH ATRIAL ORIFICE*

DURATION OF SYSTOLE (SEC.)	FLUID	ATRIAL ORIFICE SIZE		
		50 MM.²	20 MM.²	7 MM.²
		REGURG. %	REGURG. %	REGURG. %
2.5	Water	90	87	64
	30% Sucrose	90	85	69
	60% Sucrose	82	78	60
1.0	Water	77	72	55
	30% Sucrose	75	73	55
	60% Sucrose	75	67	52
0.5	Water	73	68	52
	30% Sucrose	71	68	51
	60% Sucrose	68	64	49

*Aortic orifice size, 50 mm.²; aortic pressure, 85 cm. water above atrial level. Viscosities: water = 1; 30 per cent sucrose = 3; 60 per cent sucrose = 47.

The viscosity changes introduced in these studies were large, probably far beyond any changes in the circulating blood. It is possible, however, that some combination of changes in the viscosity and plasticity of the blood may contribute significantly to the distribution between regurgitant and forward flow.

10. Effect of heart rate: Changes in heart rate may affect the celerity of ventricular contraction and the stroke output. Studies were undertaken to determine the effect of changes in rate on forward flow.

The effect of variations in the heart rate on the degree of regurgitation was studied in the model shown in Fig. 1. For comparison the output at various rates of the artificial circulation model without mitral regurgitation was used as a base line. The optimal rate for our model in terms of maximum output was found to be 30 beats per minute (Fig. 9). Faster or slower rates caused a decline in both stroke and minute output. As in the heart, it was found in the model that with increased rates above the optimum, there was encroachment upon the rapid-filling phase, reducing filling volume and hence stroke output. Also as

in the heart, so in the model using the sheep cecum for a ventricle, the filling was limited even when more time was permitted by slowing the rate so that little increase in ventricular filling occurred when the heart slowed. Hence, little increase in stroke volume developed and so the minute volume, the product of stroke volume and heart rate, declined.

When the experiments were repeated after producing mitral insufficiency, a curve with an optimal forward output at 30 strokes per minute was obtained. However, as expected, the forward flow was considerably less than that obtained when the mitral valve was intact (Fig. 9). The results emphasized that heart rate may be a critical factor in the maintenance of a forward flow and in the efficacy of the pumping system. At very slow or very fast rates the forward flow fell to vanishing values. In the experiment cited, 40 per cent of the ventricular volume was pumped forward at the optimal rate of 30 beats per minute.

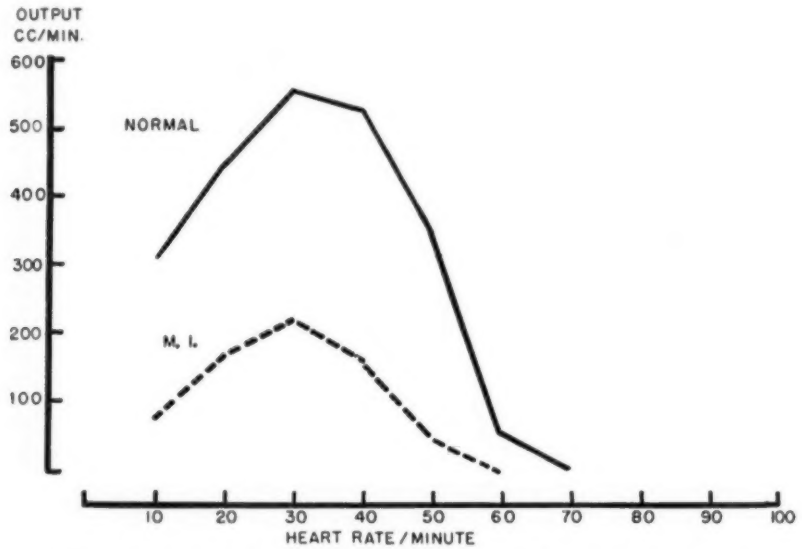

Fig. 9.—Effect of heart rate on forward flow. The model described in Fig. 1 was used. The forward output when the mitral valve closed during systole is given by the curve marked *normal*. The forward output obtained under the same conditions of ventricular filling, but with an insufficient mitral valve, is given by the dotted line labeled *M.I.* The difference between the two curves gives the degree of regurgitation for each heart rate. Discussed in text.

As the rate slowed to 20 and 10 beats per minute, the percentage of forward flow fell to 38 and 25 per cent, respectively, of the filling. Increase of the pump rate to 40, 50, and 60 beats per minute reduced the percentage of forward flow to 30, 15, and 0 per cent, respectively. In our model, and to some extent in the heart, the effect of rate, aside from effects due to celerity of contraction, is dependent on the volume filling of the ventricle. These data point up the importance of adequate ventricular filling during each diastole if an adequate forward flow is to be maintained. This depends on the atrial pressure, size of the inflow orifice, size of the ventricular chamber, the resistance to stretch of the ventricular wall, and the duration of diastole.

C. Mitral Insufficiency in a Synthetic Circulation Model.—After dealing with the sundry factors individually, an attempt was made to obtain a composite picture from a circulation model. Therefore, a synthetic circulation model previously described[16] was used. This apparatus permitted an estimate of the net effect of the interplay of some of the various factors involved. In this model, similar in principle to that shown in Fig. 1, fluid passed from the left atrium through the mitral orifice and thence into the left ventricle. Contractions of the right and left ventricle were produced by intermittent positive air pressure applied to the outer wall of the ventricles. The auricles, unlike the living heart, did not beat in this model. Details of the mechanisms utilized have already been published.[16]

Ventricular contraction produced a flow either forward against a pulsatile systemic pressure, or backward through the mitral orifice into the left atrium. Left atrial pressure was transmitted to a simulated pulmonary circulation. This consisted of a right auricle and ventricle, pulmonary artery with manometer, wide pulmonary capillaries with low resistance to flow, and pulmonary veins entering the left atrium.

Advancement of a stylet into the mitral valve prevented the ball valve from seating in its ground-glass groove.[16] With the onset of mitral insufficiency, certain changes in dynamics became apparent. Throughout systole a notable portion of the ventricular contents was regurgitated into the left atrium. The atrium became distended and a marked rise in atrial pressure synchronous with ventricular contraction was observed. This effect was heightened by the arrival of blood which had passed through the lungs.

Because of the reduced forward output during the first systole, the systemic arterial pressure tended to be somewhat lower than during the control period. With the onset of diastole, the heightened atrial pressure and volume produced an enhanced filling of the ventricle (a latex ventricle was used). The atrial pressure tended to fall almost to normal values. Further, the aortic runoff during diastole had meanwhile resulted in a lowering of the diastolic pressure below its control value. Thus, at the end of the first heart cycle, the atrial volume and pressure were slightly higher than normal, the ventricle was somewhat dilated, and the systemic blood pressure had fallen slightly. All these changes operated to compensate for the valvular defect.

During the succeeding systole, the enhanced ventricular volume was partitioned between atrium and aorta on the basis of the slightly heightened auricular pressure and the lowered arterial pressure. This resulted in an improvement in forward flow; mitral regurgitation continued, though in somewhat reduced amount.

This process continued with each succeeding beat until a new equilibrium was reached with a persisting increase in atrial pressure and in end-diastolic ventricular volume. At the equilibrium state, the forward output and systemic arterial pressure tended to return in the direction of control levels. No significant effect on the pulmonary arterial pressure or right ventricular end-diastolic volume was seen.

As a consequence of the regurgitation and the rise in left atrial pressure, the mean volume of fluid in the atrium and in the pulmonary venous system was increased. In order to replace the fluid "loss" in the pulmonary bed, more fluid was added to the circulation model. If the induced regurgitation was severe or if excess fluid was added to the system, progressive congestion of the pulmonary system, filling of the "apical" vessels of the model, and a rise in pulmonary arterial pressure were noted.

When the mitral valve was permitted to close adequately by removing the stylus impediment, the output increased to normal and arterial pressure was increased somewhat. Left atrial and pulmonary arterial pressure fell to normal levels, and pulmonary congestion was relieved within a few beats.

DISCUSSION

Our studies on the dynamics of mitral insufficiency may serve to clarify some aspects of the clinical problems brought about by structural abnormality of the valve. They also may serve as a basis for the understanding of similar conditions in which flow is divided between two alternative channels, as in tricuspid insufficiency, patent ductus arteriosus, and in septal defects. It is obvious, however, that models, regardless of how well conceived and constructed, do not imitate all the factors found in the living animal. Deductions derived from such models ultimately need to be tested in the living animal and patient.

A heightened arterial pressure is shown to reduce the forward flow in mitral insufficiency. This is in accord with the conclusions of Wiggers and Feil[7] who showed increased atrial pressure pulses when the aorta was acutely constricted. A diminution in forward flow might also be expected in conditions of aortic rigidity in which the systolic pressure is heightened. Other causes for an increased resistance to aortic outflow such as aortic stenosis can also diminish the ability of the heart to maintain an adequate forward flow.

Dilatation of the left ventricle is illustrated as an important factor in increasing the forward flow. The results show that the first volume to leave the heart regurgitates during the period of "isometroid" contraction. This serves as a kind of overhead cost without which no forward flow can be accomplished. If the ventricular volume is small or if the contraction is weak, as in premature ventricular contractions, only regurgitation may occur, and no forward flow will take place. A strong contraction of a well-filled ventricle pays the "costs of operation" under the abnormal conditions and may also provide a forward flow which can be of normal proportions. Enhanced filling of the dilated and hypertrophied ventricle is thus seen as a key adjustment to pay the extra energy costs of mitral reflux.

The increased filling of the ventricle is enhanced by a somewhat heightened pressure in the left atrium and its tributaries. When no mitral stenosis is present, the atrium can empty rapidly and easily into the left ventricle thus providing a basis for enlargement of this chamber and permitting an improved forward flow. The heightened left atrial volume is momentary, occuring during ventricular

systole, and being relieved to a great extent during ventricular diastole. Obviously, the augmented atrial systole is an important contributing factor ordinarily.

With the onset of ventricular contraction the ventricular contents are extruded through the available aortic and mitral orifices. The ability of the blood mass to flow through each of these openings depends on its deformability (viscosity and plasticity), the celerity of ventricular contraction, and the physical conditions at the orifices.

No adequate method is at present available to estimate the fluidity of the blood in vivo, but on the basis of our experiments, it is suggested that it may play a role.

The celerity of ventricular contraction operates on the tendency to regurgitation in several ways. An increased celerity would act to decrease the duration of isometric contraction and thus permit early arrival at an intraventricular pressure level sufficient for opening of the aortic valves and the production of forward flow.

Increased celerity would also increase the tendency to forward flow by reducing the time of deformation of the ventricular fluid mass. It would thereby act to increase the effects of the resistance to deformation and operate like an increase in plasticity or viscosity of the blood mass. Feil and Forward[8] have shown that the celerity of contraction is unchanged in mitral insufficiency. However, conditions which would affect the myocardium adversely, as in active rheumatic fever, might reduce the celerity of contraction and thus decrease the ability of the heart to produce forward output. Digitalis may produce some of its beneficial effects in a similar manner by increasing the celerity of contraction as it does in myosin preparations.[18]

Our studies on orifices have demonstrated that when two orifices are in close proximity the standard orifice correction factors may no longer be satisfactory. Consequently, a simple application of the formula for a single orifice to the problem of mitral regurgitation may permit serious errors in the calculation of orifice size from pressure and flow relationships.[19,20]

The data obtained from our experiments suggest that when two orifices are in proximity the flow through both tends to be reduced. However, the reduction is more marked in the smaller of two adjacent orifices. The nature of this physical principle is such as to favor aortic flow as against mitral reflux.

The nature of flow patterns through orifices seems to demonstrate clearly that the presence of a large or even medium-sized mitral regurgitant opening would result in an almost complete absence of flow through an aortic orifice which led into a higher pressure head. The conclusion must be drawn that when mitral regurgitation is present, the orifice through which it passes must be quite small. Otherwise the myocardium would be quickly overwhelmed.

Without the presence of factors which operate strongly to reduce reflux, the aforementioned physical conditions would lead rapidly to cessation of forward flow and to exitus. Several factors operate to delay this eventuality, the most important of which are those acting to reduce the size of the mitral

orifice. The increased pressure acting on the ventricular surfaces of the mitral valve during systole cause the leaflets to be pressed together. This effect is enhanced by the presence of a slight flow through the lips of the leaflets. If the orifice is small and the velocity of flow through the leaflets is great, a pressure drop which may be the order of several hundred millimeters of mercury can be produced at this site, providing a powerful closing force. This effect is a consequence of the principle of conservation of energy (Bernoulli).*

The presence of simultaneous flow through two orifices also favors flow through a larger (aortic) orifice rather than through a smaller regurgitant (mitral) orifice. Simultaneous flow through two such adjacent orifices operates to reduce the apparent size of both openings calculated in terms of effluent through each opening. However, the large (aortic) opening is only slightly affected while the flow through the smaller (mitral) opening is markedly diminished. This factor of orifice competition probably plays a significant role in the distribution of output through the adjacent openings.

Another important factor operating to reduce the size of a mitral regurgitant orifice is the poorly appreciated role of the muscular ring at the base of the mitral valves.[21-23] This ring has been shown to contract strongly at the onset of ventricular systole and thus reduce the potential reflux orifice.

Discovery of an apparently large regurgitant mitral orifice at autopsy, therefore, must be looked upon as an example of a potential opening which does not represent the actual regurgitant orifice during life.[21,24] (It may, at most, represent merely the status of the moribund patient.) This must be so since hydrodynamic considerations make it clear that even a small mitral reflux orifice has a profound effect in reducing the forward pumping action of the heart. The contraction of the mitral ring, the invoking of the physical laws governing closure of the valves during flow, and the effects of orifice competition, all militate against the overwhelming mitral insufficiency which might otherwise be expected with such a large apparent opening. The present results therefore emphasize the overwhelming danger of mitral regurgitation but also illuminate the powerful anatomic and dynamic factors ordinarily acting against such an eventuality.

SUMMARY

By using specially constructed models, the hydrodynamic factors affecting the degree of mitral regurgitation were analyzed.

Forward flow into the aorta is enhanced by increases in atrial pressure, ventricular filling, viscosity of the blood, celerity of ventricular contraction, and by lateral pressure effects on the regurgitant orifice.

The tendency to mitral regurgitation is heightened by a rise in systemic arterial pressure, an increase in the size of the regurgitant orifice, or a decrease in the celerity of ventricular contraction.

*This principle states that the energy of a unit volume of fluid may be expressed as a sum of its lateral pressure plus the square of its velocity. If the velocity is great at a point of constriction, as may occur between the lips of the mitral valve, a very great local pressure drop may be produced. The push on the ventricular walls produced by the intraventricular pressure rise, summated with the marked drop in pressure at the valve margins, serves effectively to approximate the edges of the valve and reduce the size of the regurgitant orifice.

The proximity of the aortic orifice to the mitral opening operates to reduce reflux because of competition of the two valve areas for streamlines of flow. The role of pipe competition is examined and discussed.

The relative contributions of each of the foregoing factors are reviewed in terms of findings on an integrated model of the circulation.

The significance of these findings in clinical mitral insufficiency is discussed.

We wish to acknowledge the benefit of discussions of the problem with Dr. Louis N. Katz.

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A STUDY OF THE CORRELATION BETWEEN ROENTGENOGRAPHIC AND POST-MORTEM CALCIFICATION OF THE AORTA

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IN a current study of the prevalence of atherosclerosis in a random sample of a working population over forty years of age, roentgenograms of the thoracic and abdominal aorta were made in every case. The first 568 patients studied showed radiologic evidence of calcification in 26 per cent of the men and 23 per cent of the women.[1] This unexpected finding led us to test the accuracy of our roentgen diagnoses by studying autopsy specimens of aortas from patients in whom roentgen films of the corresponding areas had been taken during life. An opportunity for such a study presented itself at Francis Delafield Hospital where roentgen films of the chest and lateral views of the lumbosacral spine are taken on most patients in a search for primary and metastatic neoplastic lesions. Dr. Edith Sproul of the Department of Pathology and Dr. Arnold Bachman of the Department of Radiology gave their cooperation and assistance.

METHODS

The roentgen films of patients recently autopsied were examined, and if a satisfactory chest or lateral abdominal film or both were available, these were reviewed for the presence of radiologic evidence of calcification of the aorta. The autopsy material was then studied without the knowledge of the individual radiologic report. In the last fifteen cases of this study only those showing calcification on the roentgen film were used. Posteroanterior chest films were taken at a distance of 6 feet at 1/20 second, using an average of 300 milliamperes and 70 kilovolts. Lateral abdominal films were taken with a Bucky grid at a distance of 40 inches, at 1-1/2 seconds, using an average of 300 milliamperes and 78 kilovolts, centering the tube at the level of the first and second lumbar spine.

Calcification of the thoracic aorta was diagnosed if a definite crescent-shaped density in the knob or a linear streak over one centimeter long in the descending portion of the aorta was visualized. A density of the aortic knob which was neither typical in shape or position was classified as questionable.

Calcification of the abdominal aorta was diagnosed in the presence of either linear densities at least one centimeter in length, or multiple and sometimes parallel linear densities, or solid shadows, in an area parallel and anterior to the lumbar spine. These films were further divided into three subgroups depending

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Received for publication April 20, 1954.

on the extent of involvement. If there was a linear streak less than one centimeter long in the proper area, the case was classed as questionable.

In reviewing pathologic material, attention was paid only to gross calcification. The specimen was carefully palpated and then incised for any plaques of cartilaginous feel. A larger plaque that cracked on bending or a smaller plaque that exuded white crystalline particles on incision, rather than soft yellowish atheromatous material, was indicative of calcification. Pathologic specimens of the thoracic and abdominal aorta were graded into three groups depending on the degree of atheromatous involvement. Discreet, small, raised lesions were considered minimal and classified as Grade 1, larger nonconfluent lesions as moderate and classified as Grade 2, and large confluent, frequently ulcerated lesions were considered as advanced and called Grade 3.

RESULTS

Roentgenograms and corresponding specimens of the thoracic aorta were available in seventy-two cases and of the abdominal aorta in fifty-five cases. The findings are summarized in Table I. Eighteen cases gave roentgenologic evidence of calcification of the thoracic aorta and all were verified at post-mortem study. Five cases were classified as questionable, and no calcification was demonstrated in any of them. In addition, four cases failing to show any radiologic evidence of calcification were found to have calcification of the thoracic aorta on pathologic examination.

TABLE I. COMPARISON BETWEEN ROENTGENOGRAPHIC AND POST-MORTEM CALCIFICATION OF THE AORTA

CALCIFICATION ON ROENTGEN FILM		TOTAL	CALCIFICATION IN POST-MORTEM SPECIMEN	
			PRESENT	ABSENT
Thoracic aorta	Present	18	18	0
	Absent	49	4	45
	Doubtful	5	0	5
Abdominal aorta	Present	20	20	0
	Absent	31	5	26
	Doubtful	4	4	0

Twenty cases were diagnosed by our criteria as having calcification of the abdominal aorta on roentgen film, and four were considered to have questionable evidence. All of these twenty-four cases were found to have calcification of the aorta on post-mortem study. In five cases, pathologically demonstrable calcifications were not visualized on the roentgen film.

The age and sex distribution of the patients in this study is shown in Table II. Persons above the age of sixty had a very high incidence of calcification of the aorta independent of sex.

In over 80 per cent of the cases in which calcification of the aorta was present on post-mortem examination, the atherosclerotic lesions of the aorta were advanced (Grade 3) while only 10 per cent of cases without post-mortem evidence of calcification had Grade 3 changes, indicating that the presence of calcification usually signifies advanced disease.

TABLE II. POST-MORTEM CALCIFICATION OF THE AORTA ACCORDING TO AGE AND SEX

AGE IN YEARS	SEX	TOTAL	CALCIFICATION	
			PRESENT	ABSENT
Below 40	Male	1	0	1
	Female	5	0	5
40-49	Male	7	4	3
	Female	7	2	5
50-59	Male	12	4	8
	Female	13	6	7
60 and over	Male	15	11	4
	Female	12	11	1
All ages	Male	35	19	16
	Female	37	19	18

DISCUSSION

A number of reports, based on isolated cases, on the radiologic appearance of calcification of the aorta have been published.[2-7] The radiologic finding of aortic calcification in an individual person seems to be of little clinical significance, since uncomplicated aortic atheromatosis causes no symptoms and does not necessarily indicate the presence of atherosclerosis in other arterial beds. In clinical studies and surveys, however, the demonstration of calcification may become a useful aid in the diagnosis of atherosclerosis,[1,8,9] even though a considerable number of cases of advanced aortic atheromata will remain undiagnosable by this method. It does not detract from the value of electrocardiography that this procedure likewise misses many instances of advanced coronary disease. Of more serious concern would be the possibility of making a false-positive diagnosis of aortic calcification. In surveying large numbers of roentgen films for evidence of aortic calcification, we occasionally experienced difficulty in deciding whether a given small density indicated the presence of an atheromatous plaque or represented calcifications in rib cartilages, lung parenchyma, spinous ligaments, or even artifacts. The data presented here give us confidence that our interpretation of these shadows is correct and that they indicate the presence of advanced aortic atheromata. Lansing and co-workers[10] have described intimal ossification in aortas from senile individuals, apparently not preceded by primary atheromatous changes in the intima. In this study, no such cases have been

encountered. Calcifications always occurred in association with atheromata. These were almost invariably ulcerated.

The fact that a number of calcifications are not visualized radiologically suggests that the technique of taking roentgen films is important in obtaining best results, as pointed out by Ungerleider.[11] A definite plaque may fail to show clearly or at all on an improperly taken film. Chest films should be slightly overpenetrated though the present study is based on softer films taken in the usual way. Exposures as used for skeletal surveys appear to be adequate for lateral views of the abdomen; some workers prefer tangential views.[9,12]

CONCLUSIONS

Roentgenologic demonstration of aortic calcification is an accurate method for the diagnosis of aortic atherosclerosis. It usually indicates an advanced degree of atherosclerosis. Although advanced atheromata are frequently missed by this method, a false-positive diagnosis was not made in a single case.

The usefulness of this method of diagnosis is pointed out. It is hoped that this study may encourage others to use these radiologic methods more extensively in clinical studies of atherosclerosis.

The authors are much indebted to Dr. Ernst P. Boas for his encouragement and advice

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STUDIES OF PULMONARY HYPERTENSION. V.

The Syndrome of Patent Ductus Arteriosus With Marked Pulmonary Hypertension

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PATENT ductus arteriosus is one of the commonest congenital malformations of the heart and great vessels and has been adequately described by many authors.[1-3] The direction of blood flow is usually from aorta to pulmonary artery because of the higher pressure in the former. The diagnosis of a typical case can be made without elaborate studies. However, atypical cases may resemble other cardiac conditions and the diagnosis may require cardiac catheterization and angiocardiography. The continuous murmur and wide pulse pressure are often absent, the right ventricle instead of the left may be enlarged, and pulmonary artery pressure may be elevated. In advanced stages reversal of flow may occur, and pronounced polycythemia and cyanosis result. These cases are unusual and constitute a clinical syndrome.[4]

In 1925, Holman[5] collected from the literature sixteen atypical cases of patent ductus arteriosus with evidence of reversed flow. In each case the right ventricle and the pulmonary artery were markedly enlarged, and in some cases visible cyanosis was present. In 1944, Chapman and Robbins[6] reported a case of patent ductus arteriosus with marked right-ventricular hypertrophy, pulmonary vascular changes, and cyanosis. Since 1947, isolated cases of patent ductus arteriosus with pulmonary hypertension and predominant right-ventricular hypertrophy have been reported,[7-20] but studies of a larger number of cases are few.[21-24,28] Two recent papers by Hultgren and associates[22] and Dammann and associates[23] describe admirably the clinical features, roentgenologic and electrocardiographic changes, and include physiologic and pathologic studies.

During the past 5 years, we have studied four patients with proved patent ductus arteriosus and marked right-ventricular hypertrophy, three of whom had severe pulmonary hypertension by cardiac catheterization. The fourth case is included because of the presence of differential cyanosis and characteristic pathologic changes in the heart and lungs. The diagnosis of patent ductus arteriosus was not suspected clinically in three cases.

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This study was supported in part by a research grant-in-aid from the National Heart Institute, National Institutes of Health (H-222 (C4)), United States Public Health Service and by the Hochstetter Fund and Ernest L. Woodward Fund.

Received for publication March 13, 1954.

In view of the likelihood of progressive pulmonary vascular changes as well as the hazards of cardiac decompensation and bacterial endocarditis in these atypical cases, and because successful surgical ligation of the ductus can sometimes be accomplished, the importance of an accurate and early diagnosis cannot be overemphasized. Our purpose is to report these four cases, to review the literature, and to summarize some of the characteristic features of this syndrome.

Methods of study are similar to those described in previous communications.[25,26] For technical reasons, no attempt is made to estimate either the systemic or the pulmonary blood flow.

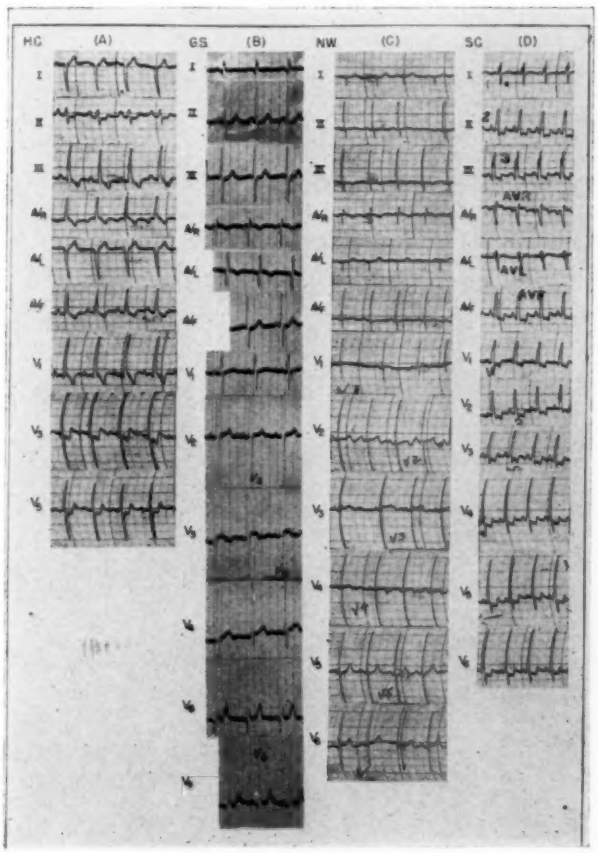


Fig. 1.—Electrocardiograms of four cases of patent ductus arteriosus with marked pulmonary hypertension. For description, see text.

CASE REPORTS

CASE 1. A 44-year-old policeman was admitted for the first time on Jan. 5, 1950. He complained of hoarseness for the past year and a half, and of dyspnea, orthopnea, easy fatiguability, and swelling of the legs for one year. During the past year he had lost 40 pounds in weight. Treatment with digitalis and low-salt diet had resulted in rapid regression of the ankle edema.

On admission the patient was well developed and nourished, plethoric, and slightly cyanotic. His voice was hoarse and there was slight clubbing of the fingers. The heart was enlarged. The

rhythm was regular with a rate of 83 per minute. A harsh, high-pitched systolic murmur was heard over the entire precordium, loudest in the fourth intercostal space at the left sternal border. A short, rumbling presystolic murmur was heard at the apex, blending into a snapping first sound. The second pulmonic sound was accentuated. Blood pressures were 108 mm. Hg systolic and 78 diastolic. There were few râles at the bases of both lungs. The liver was palpable about 2 cm. below the costal margin; the spleen was not palpable.

Hemoglobin content was 27 grams per cent; the red blood count 9.5 million per cubic millimeter; and the hematocrit, 83. A 12-lead electrocardiogram (Fig. 1, A) revealed right-axis deviation, right-ventricular hypertrophy, first degree A-V block, and right bundle branch block.

Fluoroscopy and roentgenograms of the chest (Fig. 2, A) showed an enlarged cardiac silhouette with a prominent pulmonary artery segment and possible aneurysmal dilatation of the aorta or pulmonary artery. In the oblique view the right ventricle was greatly enlarged, and the left ventricle slightly enlarged. Barium swallow showed slight displacement of the esophagus posteriorly in the region of the left atrium. The lung fields were hazy and granular with accentuated vascular markings and poor transillumination.

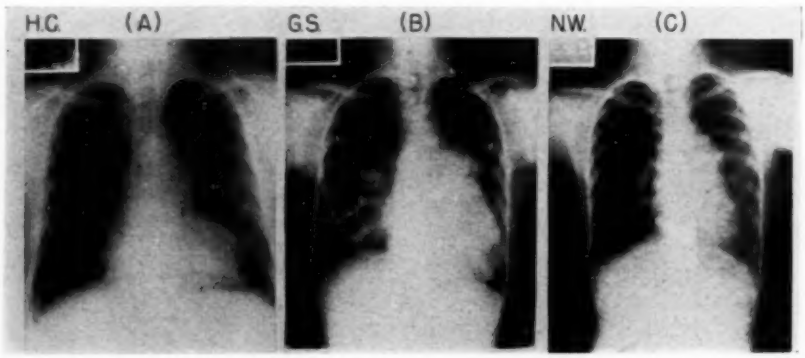


Fig. 2.—Roentgenograms of the chest of three cases of patent ductus arteriosus with marked pulmonary hypertension. For description, see text.

On Jan. 10, 1950, a phlebotomy of 500 c.c. was done. On the next day cardiac catheterization was performed and the physiologic findings are summarized in Table I. Pulmonary hypertension was severe with the systolic pressure in the pulmonary artery exceeding that in the systemic artery. The cardiac output was low and was manifested by a wide A-V oxygen difference. Arterial blood was unsaturated. The diagnosis was mitral valvular disease of rheumatic origin with polycythemia. He was discharged on Jan. 13, 1950.

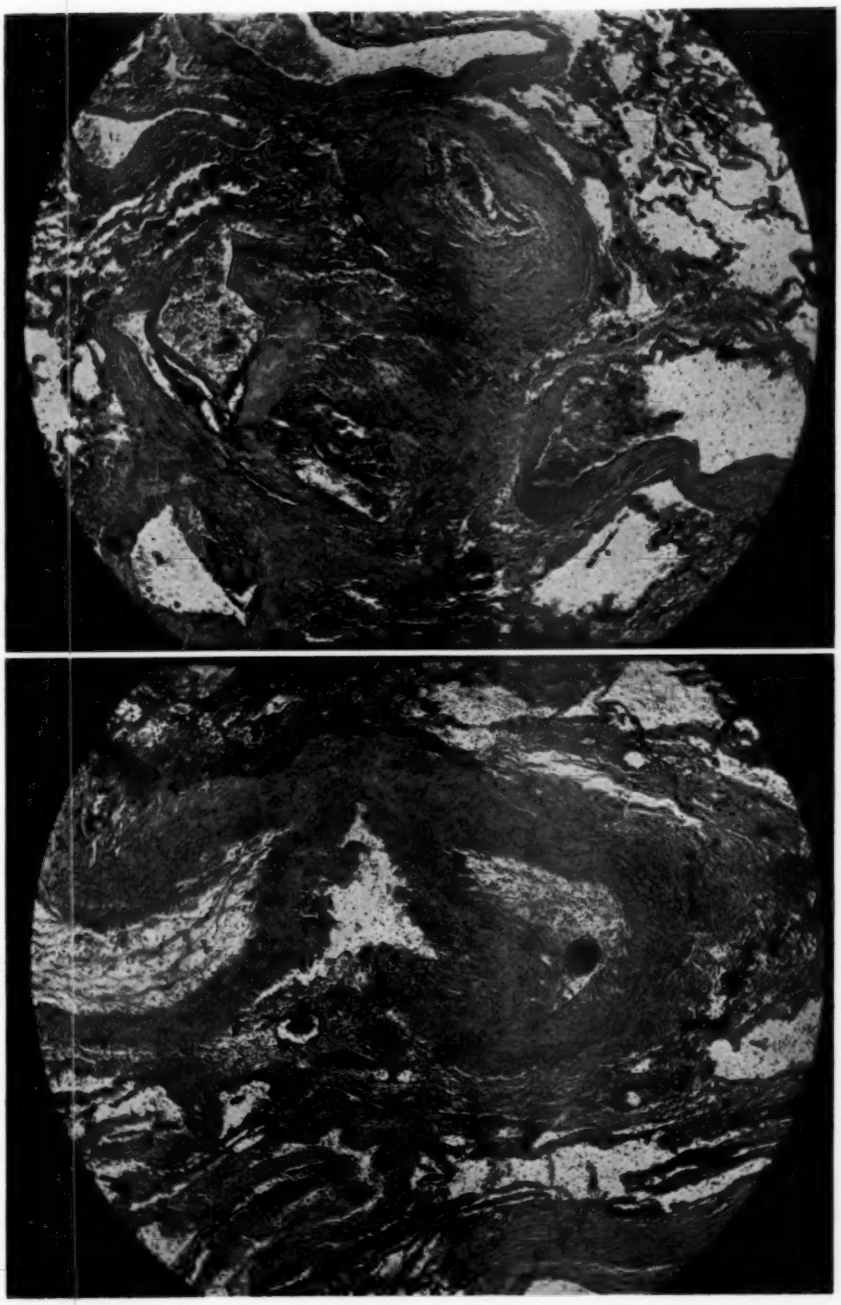
On Jan. 29, 1950, he was readmitted for phlebotomy. From Jan. 31 to Feb. 8, 1950, eight phlebotomies were performed and a total of 4,250 c.c. of blood removed.

He was admitted to Clifton Springs Sanitarium, Clifton Springs, New York, and died on Sept. 21, 1952. The pertinent findings at post-mortem examination were as follows:

The heart was greatly enlarged, weighing 600 grams, and showed extreme dilatation of the right auricle and right ventricle. Both the tricuspid and pulmonary valves were presumed incompetent because of marked dilatation of the rings. At the classic site there was a large patent ductus arteriosus. The aorta and pulmonary artery were closely adherent, and there was a large connecting opening, 1.5 cm. in diameter. The margin was jagged, irregular, and heavily calcified. In addition, there was a 3 or 4 cm. zone of calcification forming a large ring around the margin of the ductus. The pulmonary artery was greatly dilated. The left heart was small without evidence of mitral stenosis. The lungs were intensely congested but otherwise grossly unremarkable. However, histologic examination revealed advanced arteriosclerosis of pulmonary arterioles with calcification in some areas (Fig. 3, *A* and *B*). The liver was large and nodular, presumably the result of passive congestion.

Case 2. A 28-year-old housewife was first seen on Sept. 15, 1949. She described limited exercise tolerance and exertional dyspnea for six years since the birth of her only child which was

A.



B.

Fig. 3.—Photomicrographs of the lungs of patient H. C. (Case 1). For description, see text.

delivered by Caesarean section because of her cardiac condition. She suffered occasional sensations of tightness in her chest accompanied by fainting and dizziness. She frequently noticed skipped heart beats and sometimes a very rapid heart rate. A heart murmur had been heard since her infancy.

She was well developed and well nourished, rather hyperkinetic and anxious. Respiratory rate was 24 per minute, heart rate 88 per minute, blood pressure 124 mm. Hg systolic and 58 diastolic. There were no cyanosis, edema, or clubbing. The jugular veins were slightly distended. The lungs were clear. The heart was moderately enlarged bilaterally with the apical impulse at the left sixth intercostal space along the anterior axillary line. A harsh, loud continuous murmur was audible in the second and third intercostal spaces to the left of the sternum. The pulmonic second sound was accentuated.

A 12-lead electrocardiogram (Fig. 1, *B*) showed sinus rhythm, no axis deviations, and a pattern of QRS in the precordial leads compatible with left- and right-ventricular hypertrophy.

Fluoroscopy and roentgenogram of the chest (Fig. 2, *B*) showed gross enlargement of both ventricles, aneurysmal dilatation of the pulmonary artery, and accentuated pulmonary vascular markings with intrinsic hilar pulsations. The left atrium was not enlarged.

Cardiac catheterization was performed on Sept. 30, 1949, and the hemodynamic studies are presented in Table I.

TABLE I. CARDIAC CATHETERIZATION DATA IN THREE CASES OF PATENT DUCTUS ARTERIOSUS

	CASE 1	CASE 2	CASE 3
1. *Oxygen content in vol. %*			
Brachial artery	23.5 (80%)*	17.3 (98%)*	—
Femoral artery	—	—	16.5 (88%)†
Pulmonary artery	16.0	14.7	14.1
Right ventricle	—	12.6	12.2
Right atrium	—	10.5	12.2
Superior vena cava	—	12.3	13.5
Inferior vena cava	—	—	9.8

	CASE 1			CASE 2			CASE 3		
	S	D	M	S	D	M	S	D	M
2. *Pressure measurement in mm. Hg*									
Brachial artery	130	90	104	120	47	72	—	—	—
Abdominal aorta	—	—	—	—	—	—	106	72	86
"Pulmonary capillary"	—	—	—	—	—	—	—	—	9
Pulmonary artery	131	73	93	84	50	65	95	67	79
Right ventricle	131	13	—	90	10	—	101	4	—
Right atrium	—	—	—	—	—	9	—	—	3

*Figures in parentheses denote oxygen saturation.
†Blood samples obtained from abdominal aorta.

On Sept. 12, 1950, an exploratory operation was performed by Dr. E. B. Mahoney. A large patent ductus arteriosus measuring about 1 cm. in diameter was found. The proximal pulmonary artery was greatly dilated and measured at least 6 cm. in diameter in the region of the bifurcation. The aorta appeared normal in size. It was not possible to ligate the ductus because of its extreme shortness (window ductus) together with marked aneurysmal dilatation of the pulmonary artery. The patient was discharged on Sept. 23, 1950. In 1951, she moved out of Rochester and in November, 1953, we were told by her physician that she had severe dyspnea on slight exertion.

CASE 3. A 12-year-old girl had been known to have a heart murmur since the age of two years. She tired easily but kept up with her playmates. Her temperature, pulse, and respiration were normal, and her blood pressure measured 100 mm. Hg systolic and 75 diastolic. She was a tall, thin girl without cyanosis or clubbing. Examination of the heart revealed a left precordial bulge and a diffuse thrust over the left precordium, although the apical beat was well localized in the fifth intercostal space outside the mid-clavicular line. By percussion the heart was enlarged to the anterior axillary line in the fifth intercostal space. A diastolic thrill was palpable, maximal in the third intercostal space, medial to the apex and was diffusely transmitted over the precordium. A loud, harsh, rough murmur was heard throughout diastole with questionable presystolic accentuation. The murmur was loudest in the third and fourth intercostal spaces medial to the apex and was transmitted over the precordium and to the apex. No systolic murmur was heard. The second pulmonic sound was loud and snapping. A 12-lead electrocardiogram (Fig. 1, *C*) showed right-axis deviation and right-ventricular hypertrophy. Fluoroscopy and roentgenograms of the chest (Fig. 2, *C*) revealed generalized cardiac enlargement with apparent right- and left-ventricular components. There was a prominent bulge of the pulmonary conus segment as well as accentuated pulmonary vascular markings with intrinsic hilar pulsations. Barium swallow did not indicate atrial enlargement.

Cardiac catheterization was performed on March 20, 1953. The catheter was advanced into the descending aorta through a communication between pulmonary artery and aorta. With the pressure continuously recording, the catheter was slowly withdrawn through the ductus arteriosus into the pulmonary artery. As the catheter tip entered the pulmonary artery, the systolic pressure declined slightly, the diastolic pressure rose, and the pulse pressure narrowed. The aortic pressure measured 107/68 mm. Hg and as the catheter was withdrawn into the pulmonary artery the pressure changed to 96/73 mm. Hg (Fig. 4). At the conclusion of the procedure the catheter was replaced by a polyethylene tube and a cineangiocardiogram was made (Fig. 5). The hemodynamic studies are summarized in Table I.

CASE 4. A 13-year-old girl was admitted to the Genesee Hospital, Rochester, New York, on July 28, 1950, because of dyspnea, abdominal pain, nausea, and vomiting. At the age of 1½ years a pediatrician had discovered congenital heart disease. Her mother stated that the patient had had a normal childhool except for slightly limited exercise tolerance. There was no cyanosis or dyspnea until the autum of 1949, when she began to experience markedly diminished exercise tolerance. In March, 1950, she was significantly disabled and mildly cyanotic. A diagnosis was made of probable rheumatic heart disease with congestive failure. She was put to bed for six weeks and maintained on digitoxin with slight improvement.

One week prior to admission dyspnea and cyanosis increased. Five days before admission nausea and vomiting began. Two days later she complained of pain in the epigastrium and in the right upper quadrant. There was absolutely no exercise tolerance; she was tired even when turning over in bed.

On admission the patient appeared chronically and acutely ill and severely orthopneic. She was distressed by admoninal pain and dyspnea. Her toes were more cyanotic than her fingers. The heart was greatly enlarged both to left and right with the maximum impulse in the left anterior axillary line. A pronounced systolic thrill was felt in a wide area around the apex. The rhythm was regular with a ventricular rate of 86 per minute. In the mitral region a harsh, rough, Grade 4 systolic murmur was heard throughout systole. A loud, low-pitched, rough diastolic murmur was also heard at the apex. Both murmurs were conducted toward the back. Over the pulmonic area the character of the murmurs was essentially the same. The liver was enlarged and tender. Mild clubbing of fingers and toes was noticed.

Laboratory examinations showed a hemoglobin of 21.4 grams per cent and red blood count, 7.04 million per cubic millimeter. Blood urea nitrogen was 60 mg. per cent and CO_2 combining power 17 mEq. per liter. The urine contained albumin and casts. Blood culture on July 29 remained sterile. A 12-lead electrocardiogram (Fig. 1, *D*) revealed right-axis deviation and right-ventricular hypertrophy. The P waves in the standard limb leads suggested atrial hypertrophy. Frequent ventricular premature beats were noticed. Special studies, including x-rays, were considered inadvisable because of her critical condition. The clinical diagnosis was possible interatrial septal defect or Lutembacher's syndrome.

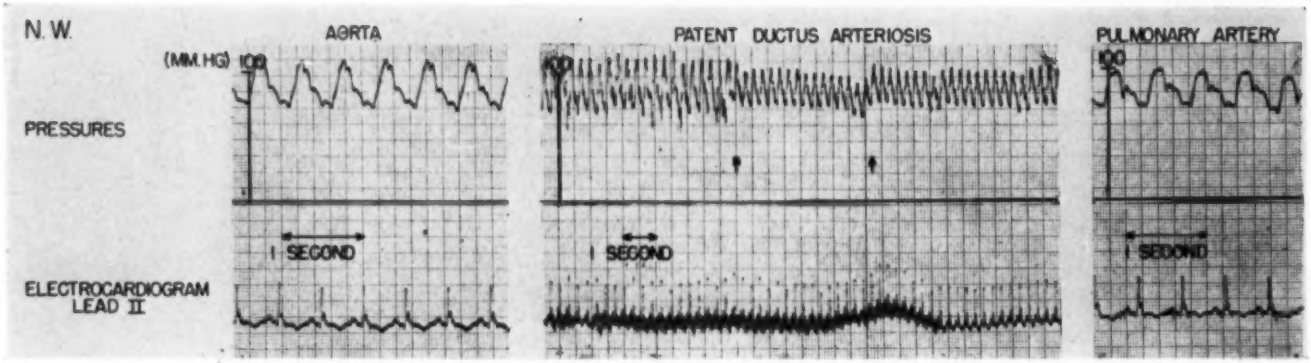


Fig. 4.—Simultaneous pressure tracings and electrocardiogram obtained during cardiac catheterization in patient N. W. The arrows in the middle tracing indicate the pressure in the patent ductus arteriosus when the catheter was withdrawn from the aorta to the pulmonary artery through the ductus.

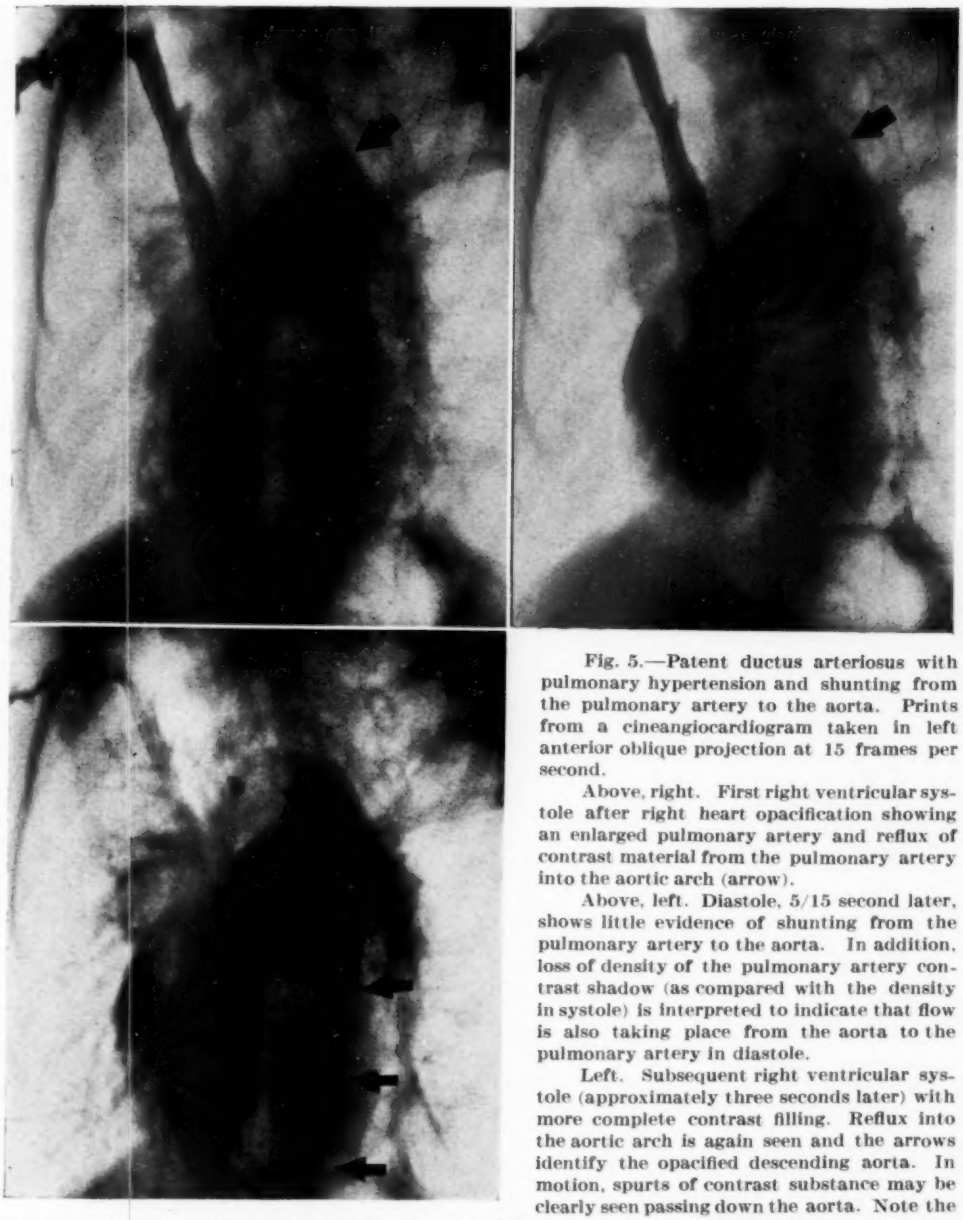


Fig. 5.—Patent ductus arteriosus with pulmonary hypertension and shunting from the pulmonary artery to the aorta. Prints from a cineangiocardiogram taken in left anterior oblique projection at 15 frames per second.

Above, right. First right ventricular systole after right heart opacification showing an enlarged pulmonary artery and reflux of contrast material from the pulmonary artery into the aortic arch (arrow).

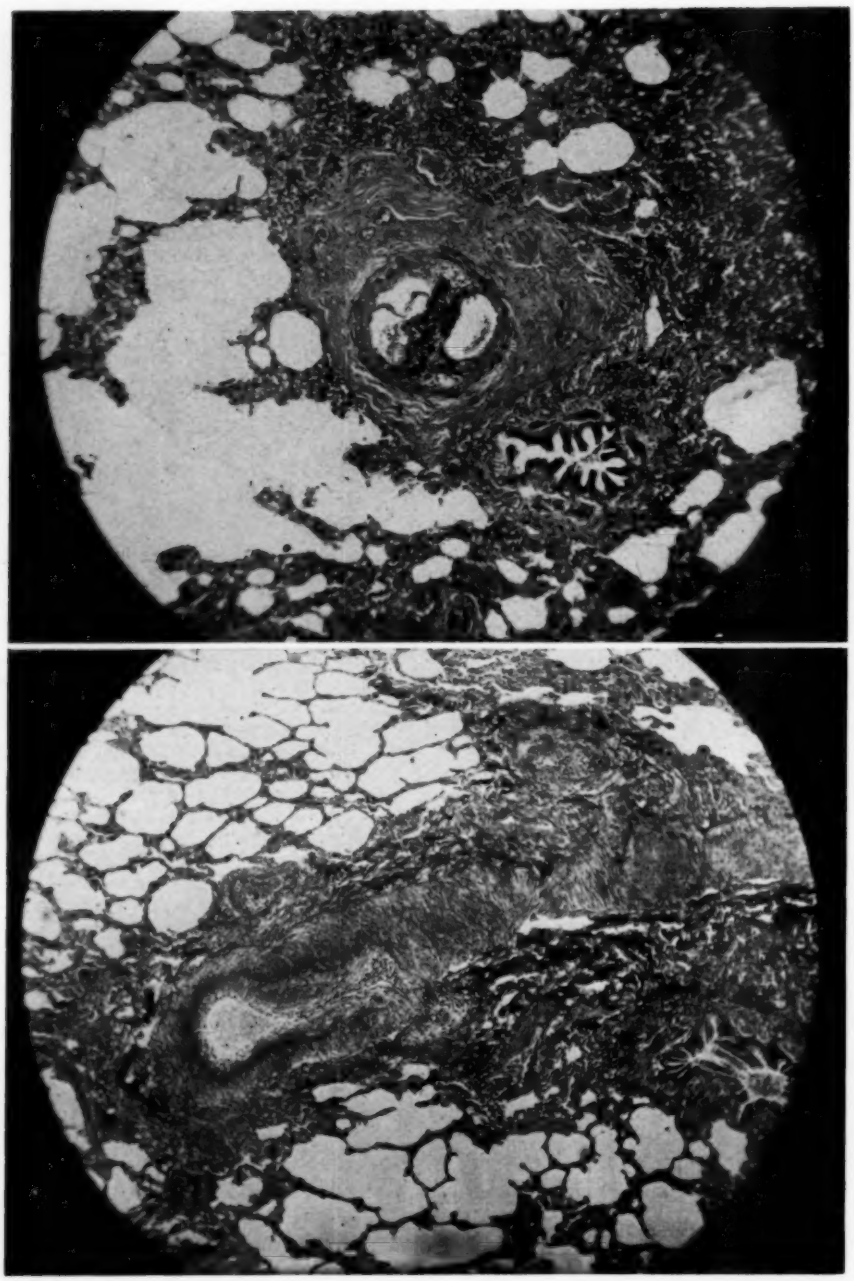
Above, left. Diastole, 5/15 second later, shows little evidence of shunting from the pulmonary artery to the aorta. In addition, loss of density of the pulmonary artery contrast shadow (as compared with the density in systole) is interpreted to indicate that flow is also taking place from the aorta to the pulmonary artery in diastole.

Left. Subsequent right ventricular systole (approximately three seconds later) with more complete contrast filling. Reflux into the aortic arch is again seen and the arrows identify the opacified descending aorta. In motion, spurts of contrast substance may be clearly seen passing down the aorta. Note the engorgement of the pulmonary vascular bed. The ductus itself is not visualized; however, it seems likely that the communication between the pulmonary artery and the aorta is a very wide one.

The hospital course was one of rapid decline. Thirty-six hours after admission moist râles were heard in the chest and the liver was larger. She became increasingly cyanotic and died on July 31, 1950.

The pertinent post-mortem findings were as follows: the heart weighted 430 grams and almost filled the left thorax. The right atrium and right ventricle were greatly dilated. There was marked hypertrophy of the right ventricle. The pulmonary artery was tremendously dilated, measuring 7.5 cm. in circumference; at its bifurcation there was a large patent ductus arteriosus, 0.2 cm. in length and 2 cm. in circumference. There was no intimal lesion in either the pulmonary artery or aorta in this region. Grossly the lungs showed only moderate congestion and dilatation of the pulmonary arteries. The liver, weighing 770 grams, exhibited the nutmeg pattern of passive congestion.

A.



B.

Fig. 6.—Photomicrographs of the lungs of patient S. C. (Case 4). For description, see text.

Histologic examination: (Fig. 6, *A* and *B*). The lungs were moderately atelectatic with some thickening of the alveolar walls. The main lesions were vascular. The capillaries and venules were generally normal except for distention, although a few showed slight hyalinization of their walls. There was marked fibrous tissue proliferation of the intima of arteries and arterioles, and in many cases hyalinization. In some vessels this fibrosis was spotty; in others it included the entire intima. In many, intima constituted one-half or more of the thickness of the vessel wall. The lumen of a few arteries was obliterated by this process. In a few, organizing thrombi were seen. An occasional vessel had recanalized. In general, the media were not involved. Normal elastic fibers were present in the arteries. The liver showed marked congestion of the central areas with atrophy of parenchymal cells. All other organs were essentially normal without vascular lesions. The lungs were also studied from macerated casts of the pulmonary vessels injected with colored vinyl acetate[27] (Fig. 7). When compared with the vascular cast from a normal lung of comparable age, the smaller branches of the pulmonary artery from this case were not filled, although the pulmonary veins were equally well filled in both cases. Inability to fill the smaller branches of the pulmonary artery correlated directly with occlusion of the lumina of these vessels as demonstrated in histologic section. Similar observations have been made by Hultgren and associates,[22] and by Holman and associates.[20]

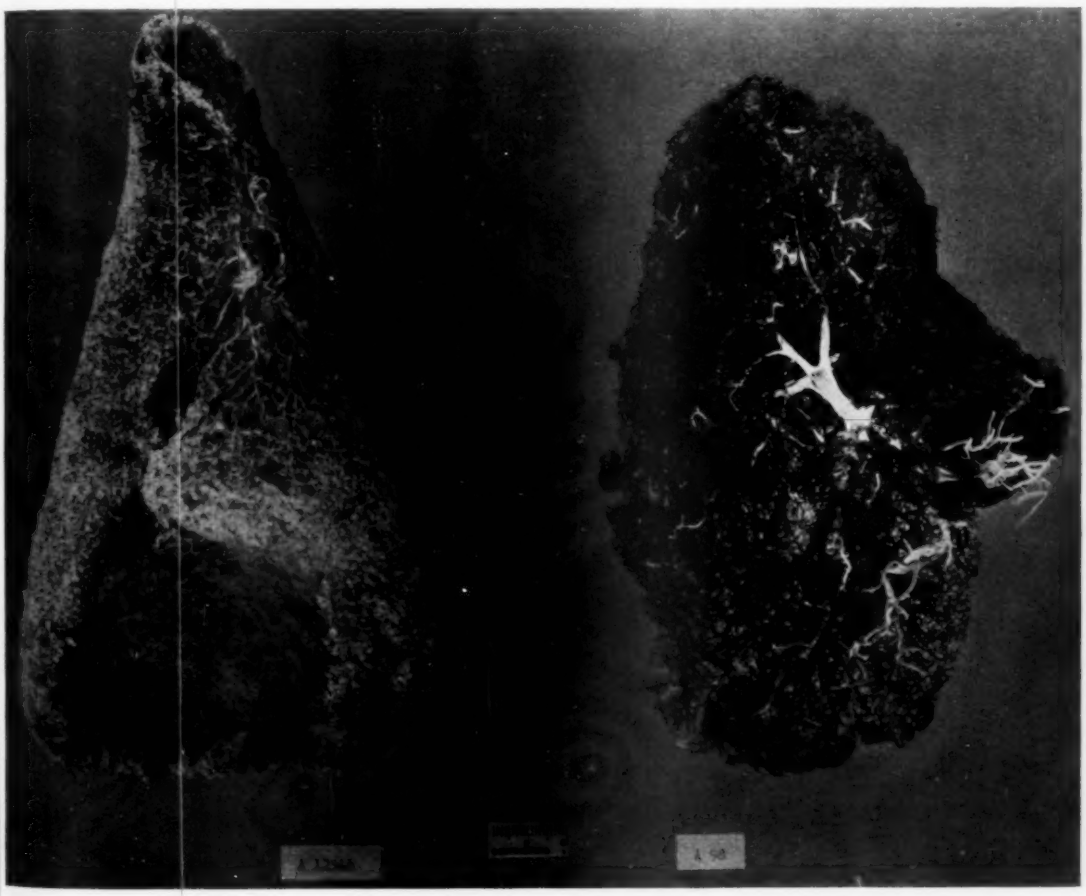


Fig. 7.—Photograph of the casts of the pulmonary artery (white) and pulmonary veins (black) from the left lung of a 17-year-old male, who died from cerebral concussion (left) and that from patient S. C. who had a patent ductus arteriosus with marked pulmonary hypertension (right). Note the normal filling of the branches of both the pulmonary artery and veins in the normal lung. In the lung of patient S. C. the branches of pulmonary veins filled normally but only the larger branches of the pulmonary artery were filled by the injected vinyl acetate. (× 3/8) (By permission of Dr. Charles E. Tobin and Surgery, Gynecology and Obstetrics[27]).

SUMMARY OF CASES

All four patients complained of easy fatigue and exertional dyspnea. Two demonstrated generalized cyanosis and clubbing of the extremities, which were more pronounced in the lower extremities of one. Cardiac enlargement and accentuation of the second pulmonic sound occurred uniformly. A continuous murmur was heard in only one instance. The electrocardiograms of three showed right-axis deviation and right-ventricular hypertrophy; one exhibited normal-axis and combined ventricular hypertrophy. X-ray studies of three patients revealed enlargement of the pulmonary artery and right ventricle with accentuation of pulmonary vascular markings. Left-ventricular enlargement and intrinsic hilar pulsations were each seen twice. Cardiac catheterization of three patients revealed pronounced pulmonary hypertension in all and normal pulmonary-artery wedge or pulmonary "capillary" pressure in the single case in which it was measured. Two had unsaturated arterial blood, indicating reversed shunt. Angiocardiography in one instance showed simultaneous early filling of pulmonary artery and descending aorta. Postmortem examination of two cases revealed structural abnormality of pulmonary arterioles in each.

TABLE II. SUMMARY OF IMPORTANT CLINICAL, PHYSIOLOGIC, AND PATHOLOGIC FEATURES IN 41 CASES OF PATENT DUCTUS ARTERIOSUS WITH MARKED PULMONARY HYPERTENSION

	NO. CASES	%
I. *Clinical features* (41 cases)		
a. Age		
Between 8 months and 5 years	9	22
Between 5 and 16 years	11	27
Above 16 years	21	51
b. Age at which heart disease was first discovered		
Under 1 year	12	29
Between 1 and 5 years	9	22
Between 5 and 16 years	7	17
Above 16 years	3	7
Not stated	10	25
c. Outstanding symptoms		
Exertional dyspnea	34	83
Easy fatiguability	29	71
Hemoptysis	6	15
Swelling of legs	12	29
d. Pertinent physical and laboratory findings		
Cyanosis	15	37
Clubbing	8	20
Rough precordial systolic murmur	32	78
Blowing diastolic murmur along LSB*	25	61
Mid-diastolic or presystolic murmur at apex	7	17
Accentuated pulmonic second sound	31	76
Gallop rhythm	3	7
Wide pulse pressure	15	37
Signs of congestive heart failure	14	34
Polycythemia	16	39
II. *Electrocardiographic changes* (41 cases)		
a. Right-axis deviation	25	61
Left-axis deviation	3	7
b. Right ventricular hypertrophy	25	61
Combined ventricular hypertrophy	12	29
III. *Roentgenologic findings* (41 cases)		
a. Enlarged right ventricle	25	61
b. Prominent pulmonary conus	28	68
c. Increased hilar vascular markings	32	78
d. "Hilar dance"	12	29

(*Continued on opposite page.*)

TABLE II—CONT'D

	NO. CASES	%
IV. *Cardiac catheterization data* (36 cases)		
a. Pressure†		
$PA_s > BA_s$	14	39
$PA_d > BA_d$	21	51
b. Significant difference in oxygen content‡		
PA blood > RV blood	24	67
BA blood > FA blood	14	39
c. Direction of blood shunt		
Predominantly from left to right	20	55
Predominantly from right to left (reversed flow)	14	39
Not definite	2	6
V. *Pathology* (14 cases)		
a. Gross findings		
Right ventricular hypertrophy	14	100
Dilated pulmonary artery	14	100
Atheroma of main pulmonary arteries	7	50
Impingement plaque on aorta	3	21
Impingement plaque on pulmonary artery	2	14
b. Histologic findings in pulmonary vessels		
Intimal proliferation and medial hypertrophy	14	100
Organized or organizing thrombi	7	50
VI. *Result of ligation of ductus* (21 cases)		
Improved	14	66
Not improved	2	10
Dead	5	24

*LSB = left sternal border
†Pressures
PA_s = pulmonary artery systolic
BA_s = brachial artery systolic
PA_d = pulmonary artery diastolic
BA_d = brachial artery diastolic

‡Blood samples from
PA = pulmonary artery
RV = right ventricle
BA = brachial artery
FA = femoral artery

REVIEW OF LITERATURE

A search was made to discover all cases with patent ductus arteriosus and marked pulmonary hypertension in the English literature from 1944 to 1953. The arbitrary criteria adopted for selection of cases were (a) pulmonary artery mean pressure above 60 mm. Hg by cardiac catheterization, and (b) right ventricular hypertrophy by clinical or pathologic examination. A few cases were not studied by cardiac catheterization, but shunt reversal was definite, indicating that marked pulmonary hypertension must have been present. Forty-one cases, including four of our own, fulfilled these criteria. Table II lists the salient historical, clinical and laboratory findings of these patients, together with the number of cases in which each was stated to be present.

The clinical, physiologic, and pathologic features of the syndrome of patent ductus arteriosus with marked pulmonary hypertension and right-ventricular hypertrophy differ from those in classical cases of uncomplicated patent ductus. Cardiac abnormality is usually discovered before puberty. The most frequent symptoms are exertional dyspnea and easy fatiguability. Occasionally patients

exhibit hemoptysis, chronic cough, and swelling of the legs. The pertinent physical findings include accentuation of P_2, a rough systolic murmur over the precordium, a blowing diastolic murmur along the left sternal border, cyanosis and clubbing of the fingers. With permanent reversal of blood flow, cyanosis of the feet may occur with little or none in the hands and face. Polycythemia is observed in many patients. The continuous machinery murmur is usually absent and an apical mid-diastolic murmur occurs occasionally. Wide pulse pressure is recorded in about one-third of the patients. The blowing diastolic murmur is probably caused by insufficiency of the pulmonic valve. About one-third of the cases exhibit congestive heart failure with or without gallop rhythm.

The electrocardiogram usually shows right-axis deviation and right ventricular hypertrophy. Combined ventricular hypertrophy occurs in about one-fourth of the cases. Roentgenograms and fluoroscopy of the chest almost always reveal a prominent pulmonary conus and enlarged right ventricle. The hilar vascular markings are accentuated, although intrinsic hilar pulsation is demonstrable in less than one-third of the patients.

Physiologic studies by cardiac catheterization reveal marked pulmonary hypertension, the pressure in the pulmonary artery in some cases exceeding that in the systemic artery.

In more than one-half of the cases the direction of blood flow is predominantly from aorta to pulmonary artery, and in more than one-third the shunt is reversed. In the latter group the difference in oxygen content of blood samples from right ventricle and pulmonary artery may be small or absent. Intermittent reversal of blood flow has been reported in several cases. Reversal of flow depends upon higher oxygen saturation of blood obtained from the right brachial artery than that from a femoral artery. This discrepancy may be accentuated with exercise.

Angiocardiograms were made in only a few cases and a general statement cannot be made. However, in one of our cases the angiocardiogram revealed reflux of contrast material from the pulmonary artery into the aortic arch after the first and subsequent right ventricular systolic ejections. The presence of patent ductus arteriosus in this case was confirmed by catheterization of the descending aorta via the ductus. Dammann and Sell[21] have commented on the diagnostic value of angiocardiography: "Recent experience in the cardiac clinic suggests that angiocardiography may be of aid in the diagnosis of patent ductus with pulmonary hypertension. Opacification of the descending aorta immediately after or simultaneously with main pulmonary arteries suggests a shunt through a patent ductus from pulmonary artery to aorta."

Pathologic changes are quite characteristic. The right ventricle is hypertrophied and dilated, and the left ventricle frequently shows minimal enlargement. Taussig[4] states that this syndrome is frequently associated with malformations of the left side of the heart, such as underdevelopment of the left ventricle and mitral stenosis. The pulmonary arteries are enormously dilated and atheromatous changes are usually evident. Histologically, intimal proliferation and medial hypertrophy of arterioles occur uniformly. Organized or

organizing thrombi are found in about one-half the cases. By injection technique, the pulmonary arterial tree in the few cases reported shows obliteration of the normal vascular architecture in the periphery.[20,22]

Surgical closure in twenty-one cases of patent ductus arteriosus with marked pulmonary hypertension resulted in definite improvement in fourteen cases, no improvement in two cases, and death in five cases. Of the last group, three patients died immediately after operation, one 7 days after operation, and one 6 months after operation.

DISCUSSION

The shunt through a patent ductus may occur during both systole and diastole. Blood flow may be from the aorta to pulmonary artery or vice versa, depending upon the gradient of pressure. When pulmonary artery pressure constantly exceeds aortic pressure, flow from the former to the latter is sustained. However, reversal of flow does not occur in every case of patent ductus with marked pulmonary hypertension. In some cases, intermittent reversal of blood flow may occur, particularly after exertion, violent cough, crying or while breathing low-oxygen concentrations.[13,14] Under these circumstances, pulmonary artery pressure is significantly elevated.

Whenever blood flow is predominantly from pulmonary artery to aorta, the following characteristic features are present: (a) pressure in the pulmonary artery exceeds that in the aorta, (b) oxygen content of blood from the right-brachial or radial artery exceeds that of blood from the descending aorta or femoral artery, particularly after exercise, so that cyanosis and clubbing may be observed in the lower extremities but not in the upper, and (c) simultaneous opacification of the pulmonary artery and descending aorta is seen in the angiocardiogram.

As pointed out previously,[25,26] pulmonary hypertension may be physiologically postcapillary or precapillary in origin. Postcapillary pulmonary hypertension occurs in patients with an increase in left-atrial or pulmonary venous pressure because of impaired blood flow into or through the left side of the heart (mitral stenosis, left ventricular failure, or constrictive pericarditis). Some investigators[18] have suggested that pulmonary hypertension in atypical cases of patent ductus arteriosus may result from increased blood flow through the left side of the heart which may elevate pressure in the left atrium with consequent pulmonary hypertension. However, a postcapillary mechanism appears unlikely in the absence of obstruction to flow through the left side of the heart or left-ventricular failure. This is supported by the recording of normal pulmonary-artery-wedge or pulmonary "capillary" pressure in one of our cases and in some cases studied by Swan and associates.[28]

Precapillary pulmonary hypertension is usually encountered in patients with (a) disproportion between the increased pulmonary blood flow and capacity of the pulmonary vascular bed, or (b) organic and/or functional changes in the pulmonary vascular bed associated with an increase in pulmonary arteriolar resistance. We agree with Hultgren and associates[22] that augmented pulmonary blood flow per se is probably not a major factor in the genesis of pulmonary

TABLE III. DIFFERENTIAL DIAGNOSIS

	PATENT DUCTUS ARTERIOSUS WITH PULMONARY HYPERTENSION	EISENMENGER'S COMPLEX	INTERATRIAL SEPTAL DEFECT	MITRAL STENOSIS
Cyanosis	None or slight in the early stage, marked in the late stage	None or slight in the early stage, marked in the late stage	Usually none	Usually none
Atrial enlargement	Not prominent	Not prominent	Usually right	Usually left
Cardiac catheterization				
(a) pressure PA*	Markedly elevated	Markedly elevated	Normal to moderately elevated	Slightly to markedly elevated
"PC"	Normal	Normal	Normal	Elevated
(b) possible difference in blood oxygen content*	PA > RV BA > FA	RV > RA	RA > VC	None
(c) abnormal communications	Pulmonary artery and descending aorta through ductus	Ascending aorta and right ventricle; right ventricle and left ventricle	Right atrium and left atrium	None
Angiocardiogram	Simultaneous opacification of pulmonary artery and descending aorta	Interventricular shunt; simultaneous opacification of pulmonary artery and ascending aorta	Interatrial shunt	No shunt

*Pressures and blood oxygen content
PA = pulmonary-artery
RV = right ventricle
FA = femoral artery
VC = vena cava
"PC" = pulmonary "capillary" or pulmonary-artery wedge
BA = brachial artery
RA = right atrium

hypertension in atypical cases of patent ductus arteriosus. In many uncomplicated classical cases there is a sustained increase in blood flow from aorta to pulmonary artery, with normal or only slightly elevated pressure in the pulmonary circuit. In the series reported by Storstein and associates,[18] blood flow in the pulmonary artery was three times that in the systemic artery in three instances, but moderate pulmonary hypertension was observed in only one case. Furthermore, no significant correlation has been found between pulmonary blood flow and pulmonary artery pressure.[22] In certain reported cases marked pulmonary hypertension and cyanosis occurred at the age of only one or two years.

It is uncertain whether permanent vascular changes in the lung are produced by a sustained increase in pulmonary blood flow. Welch and Kinney[29] found that significant atherosclerosis of the pulmonary artery is unusual in typical cases of patent ductus arteriosus under the age of 40. However, with preexistent organic restriction of the pulmonary vascular bed, increased pulmonary blood flow will undoubtedly cause further elevation of pulmonary artery pressure.[7,30]

Increase in pulmonary arteriolar resistance due to organic and/or functional changes is probably the most important factor in producing marked pulmonary hypertension in these patients. The increased pulmonary arteriolar resistance may be produced by one or more of the following three conditions:

(a) Structural changes of the pulmonary arteries and arterioles. In every case at autopsy moderate or severe structural alteration of the pulmonary vascular tree was found. In a few cases, including one of our own, injection or perfusion studies revealed striking obliteration and narrowing of the smaller pulmonary arterioles. Other changes such as multiple pulmonary thrombi and antecedent pulmonary arteritis with vascular obstruction may also play an important role in a certain number of cases.[22]

(b) Persistent high fetal pulmonary vascular resistance. This possibility was originally suggested by Edwards[30] as one of the underlying mechanisms to explain the marked pulmonary hypertension in infants and children with atypical patent ductus. However, many patients do well in childhood and adolescence and became progressively incapacitated in early adult life. It is possible, of course, that a single factor does not cause pulmonary arteriolar disease in all cases. Marked reduction of the pulmonary artery pressure shortly after ligation of the ductus has been reported in a few cases,[11, 12, 16, 18, 20-22] indicating that changes in the pulmonary vascular bed are not entirely irreversible.

(c) Vasoconstriction of the pulmonary arteries and arterioles. Studies by Burchell and associates[24] have demonstrated that the magnitude and occasionally the direction of the shunt between aorta and pulmonary artery may be altered by varying the oxygen tension in the inspired air. It is possible that increased pulmonary arteriolar resistance may be attributed in part to functional changes such as chronic anoxia or hypervolemia. The former may produce constriction or spasm of the small pulmonary arteries and the latter engorgement of pulmonary vessels. Whatever the mechanism, the available evidence indicates that pulmonary hypertension in this syndrome is precapillary in nature.

Patent ductus arteriosus with marked pulmonary hypertension may be confused clinically with Eisenmenger's complex, interatrial septal defect, and mitral stenosis. Differential observations summarized in Table III may help distinguish one condition from the other. The differentiation in some cases is uncertain and a definite diagnosis may only be made at post-mortem examination.

The decision to ligate the ductus in these patients may be difficult. It is generally agreed that sustained reversal of blood flow contraindicates ligation of the ductus. Here the ductus serves as an "escape" for the marked pulmonary hypertension and the operative mortality is high. On the other hand, if there is no evidence of shunt reversal, surgical intervention may be considered despite pulmonary hypertension. As indicated above, remarkable subjective and objective improvement has then occurred following ligation of the ductus. In a few cases, significant reduction of the pulmonary artery pressure occurred postoperatively, even though biopsy of the lung at the time of operation showed moderate structural changes in the pulmonary vessels which were presumed to be irreversible.[16,17]

SUMMARY AND CONCLUSIONS

1. Four cases of patent ductus arteriosus with severe pulmonary hypertension are reported and present a recognizable syndrome.

2. The clinical, physiologic, and pathologic characteristics of atypical patent ductus arteriosus are presented from a review of the literature.

3. The dynamics of blood flow through the ductus is discussed, and the recognizable peripheral manifestations with shunt reversal are emphasized.

4. The pathogenesis of pulmonary hypertension, probably precapillary in these cases, is discussed.

5. The favorable effect of ligation of the ductus in selected cases is cited, emphasizing the need for diagnosis before pulmonary hypertension and pulmonary vascular disease become severe and before sustained shunt reversal occurs.

We are grateful to Dr. G. J. Copeland, Director of Laboratories, the Clifton Springs Santarium and Clinic, Clifton Springs, N. Y., for the autopsy findings in Case 1 and to Dr. Edward Mulligan, formerly resident in Pathology, Genesee Hospital, Rochester, N. Y., for the pathologic examination in Case 4. We wish to thank Dr. R. Gramiak, Assistant Resident in Radiology, Strong Memorial Hospital, Rochester, N. Y., for the preparation and interpretation of the cineangiocardiogram in Case 3. We are indebted to Dr. Charles Tobin, Associate Professor of Anatomy, University of Rochester School of Medicine and Dentistry, for the studies of macerated cast of the lung in Case 4.

The technical assistance of Mr. S. John Vernarelli and Miss Carol Gouverneur and the secretarial aid of Mrs. Julia N. Gooding are gratefully acknowledged.

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THE SPATIAL VECTORBALLISTOCARDIOGRAM

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BALLISTOCARDIOGRAPHY since its inception has been concerned primarily with the motion of the body in its longitudinal axis (headward-footward). The design of the ballistocardiographic table was such that only one degree of freedom was permitted. However, Starr and Friedland[1] in investigating the respiratory variations of the ballistocardiogram, placed the subjects on a high-frequency table in various positions to obtain recordings of the motions of the body in other planes. Nickerson and Curtis[2] using the low-frequency, critically damped table placed the subject at various angles to the direction of the motion of the bed and found that no position gave a greater deflection than was given by the body lying parallel to the direction of recording (longitudinal axis). Beyond that they did not report any investigation of the spatial vector forces involved in the ballistocardiogram. Hamilton and associates[3] using a high-frequency table recorded motion in three directions simultaneously and published curves to show the directions of the movement of the body in the three principal axes. In 1950, Scarborough and co-workers[4] made a study of the motions of the body in their various spatial relationships. They employed a high-frequency table with a revolving turntable and investigated the cardiac ballistic forces in various planes. Franzblau and associates[5] used a similar method with the critically damped table. A table with two degrees of freedom, headward-footward, and lateral was designed by Braunstein and associates.[6] Brandt and associates[7] employed a direct-body coil and magnet pickup and studied the longitudinal, lateral, and dorsoventral ballistocardiograms. Rotational movements of the body have been described by Ernsthausen and colleagues,[8] utilizing a torsion ballistocardiograph. Recently Siblia[9] described a simple direct-body ballistocardiograph which recorded the body motion in three directions from a single point in the mid-axillary line at the level of the xiphoid.

The human body, a complex mechanical system, is thrown into forced vibration by auricular and ventricular contractions as well as by hydraulic forces in the vessels. The driving force of the heart and vessels is impressed on the body consisting of a rigid skeletal system and elastic soft tissue. These tissues have their own natural frequency of vibration subject to damping due to energy dissipated by friction and other resistances. When an elastic system free from impressed forces is disturbed from its equilibrium position, vibration occurs. Fundamental to this vibration are the natural frequency of the system and the rate of decay of the amplitude. The natural frequency is dependent mainly

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Received for publication Nov. 4, 1953.

on the mass and elasticity of the system, and in most cases, is only slightly affected by damping.[10] Thus the body is an elastic system forced into vibration by the dynamic force of the circulatory apparatus and subject to viscous damping. Inasmuch as one is dealing with an elastic system, an infinite number of coordinates are necessary to describe the translatory motion. It is obvious that the body is capable of vibrating in an infinite number of ways and can assume various-shaped patterns during vibration. In general, a system with more than one degree of freedom will vibrate in a complex manner wherein the amplitude and frequency appear to follow no definite pattern. However, among such multitudes of unorderly motions, there will be some special types of simple and orderly motion called principal modes of vibration, whereby each point in the system follows a definite pattern of equal frequency. Moreover, it can be shown that the more general type of motion can always be represented by the superposition of principal modes of vibration. A system of n degrees of freedom will have n principal modes with n natural frequencies.[10] In general to study the motion of the body in all possible degrees of freedom would be unduly laborious and unessential. The recording of the three principal planes of translatory motion, namely headward-footward, lateral, and anteroposterior would suffice.

MATERIAL AND METHODS

Twenty-five normal subjects were selected ranging in age from 16 years to 56 years, 15 males and 10 females. Normality of the cardiovascular system was based on the usual clinical examination, 12-lead electrocardiogram, chest roentgenogram, urinalysis, and hemogram. The electrical position of the heart was determined by the criteria set forth by Wilson and his associates[18] and was correlated with the anatomic position determined by fluoroscopy. In the twenty-five normal subjects of this study there was complete correlation between electrical position of the heart and anatomic position as disclosed by vertical fluoroscopy. Other observers[20,21] have found similar close correlation in normal hearts. It should be noted that the electrical position was obtained with the patient in the supine position. There were five individuals with electrically vertical hearts, ten with semivertical, four with intermediate, four with semihorizontal, and two with horizontal hearts. No attempt was made to secure a basal state. All tracings were taken in the recumbent position with respiration suspended in mid-inspiration.

A four-channel Polyviso oscillograph was utilized to record simultaneously the motion of the body in the headward-footward, lateral, and anteroposterior direction as scalar quantities together with Lead I of the electrocardiogram. The output of each channel of the Polyviso inscribing the ballistocardiogram was fed to the plates of the cathode-ray oscilloscope through a suitable amplifier. The output of the channel recording the electrocardiogram was fed into a trigger circuit which actuated a solenoid at the peak of the R wave of the electrocardiogram. The solenoid tripped the shutter of a 16 mm. motion picture camera which photographed the face of the cathode-ray tube for a period of 2 seconds at 24 frames per second. A lag of 0.1 second was present between the peak of

the R wave and the first frame recorded by the motion picture camera. Each of the galvanometers was standardized so that 1 mv. produced a 1-cm. deflection. The sensitivity of the cathode-ray oscilloscope was adjusted so that a 1-mv. signal impressed on the input of the Polyviso deflected the beam of electrons 3 inches, when the signal was applied to either the horizontal or vertical plates. The ballistocardiograph was of the direct-body type. Since calibration of this type of ballistocardiograph is difficult and unsatisfactory, it was not performed. However, some comparison of the ballistocardiograms in the three different directions of body motion may be made because the transducer and sensitivity of the galvanometers were identical electrically. A transducer and filter system having identical characteristics were used to inscribe motion of the body in each direction. This consisted of an iron-core coil, an Alnico V magnet, and an L-section filter having 2.5 millihenry chokes in each lead and a 25 microfarad condenser shunting the pickup coil. The ballistocardiogram produced with this transducer and filter system lags a pure velocity ballistocardiogram by 45 degrees. In each instance, the coil was placed 10 mm. from the magnet. The connection of the pickup coils to their respective galvanometers was made so that relative motion of the magnet away from the coil produced a positive or upward deflection of the galvanometers, a downward deflection of the electron beam on the X axis of the cathode-ray oscilloscope, and movement of the spot to the observer's right in the case of the Y axis.

In the scalar ballistocardiogram for recording headward-footward direction of body motion a magnet was mounted on a wooden bar which was fixed to the shins by means of elastic bands. For recording lateral motion of the body, a magnet was placed at the middle of a wooden bar, measuring 18 inches long by 2 inches wide, which was attached to the body at the left mid-axillary line by elastic bands. The bar was applied so that in each individual the position of the magnet was one inch above the crest of the ilium. To facilitate the recording of the motion of the body in the anteroposterior direction, a hinged arrangement was utilized. A magnet was fastened at one end of the light-weight, rigid, plastic bar, the other end of which was fastened to a suitable support by means of a hinge. The free end of this hinged bar with magnet was then placed upon the subject at the midsternal line one inch cephalad to the xiphoid. The coil was mounted to a rigid support exactly opposite to the magnet. The sites selected for recording the anteroposterior and lateral body motions were chosen after trial of many positions. The sites used were those where the amounts of torsional changes were considered least and amplitudes of the waves were found satisfactory.

In recording the scalar ballistocardiogram, a positive deflection of the galvanometer was produced by each of the following motions of the body: Headward, rightward, and posteriorly.* The vectorballistocardiograms representing

*These studies were performed and completed before publication of the reports of the Committee on Ballistocardiography of the American Heart Association. The recording of the scalar ballistocardiogram conforms with the conventions proposed by the Committee except for the recording of the lateral motion. Throughout this study a uniformity of recording was achieved by making all relative movement of the magnet away from the coil as a positive (upward) deflection by the galvanometer. The vector loops inscribed directly on the cathode-ray oscilloscope are in accord with conventions in current use in spatial vector electrocardiography, where a deflection of the electron beam downward and to the observer's right denotes postivity.

motion of the body in the frontal, sagittal, and transverse planes were recorded successively on the cathode-ray oscilloscope. To obtain the loop for the frontal plane the signal from the headward-footward pickup was impressed on the vertical plates and that of the lateral pickup was impressed on the horizontal plates. A headward body motion caused the electron beam to be deflected downward, and a motion of the body to the right moved the beam to the observer's right. To obtain the loop for the sagittal plane the signal from the headward-footward pickup was impressed on the vertical plates and the signal from the anteroposterior pickup was impressed on the horizontal plates. Headward motion of the body deflected the beam downward, and posterior motion deflected the beam to the observer's right. To obtain the loop for the transverse plane the signal from the anteroposterior pickup was impressed on the vertical plates, and that from the lateral pickup on the horizontal plates. Motion of the body posteriorly deflected the beam of electrons downward, and a rightward motion of the body caused the beam of electrons to move to the observer's right (Fig. 1).

The scalar ballistocardiograms for each direction of the body motion were studied qualitatively for wave form. The onset of the R wave of the electrocardiogram and its temporal relationship to the peak or nadir of the principal waves of the ballistocardiogram were measured.

By using the headward-footward ballistocardiogram as a basis, corresponding waves in the lateral and anteroposterior ballistocardiogram were compared. In each tracing a base line was constructed, from which peaks and troughs of the waves were measured. In addition, from the three scalar ballistocardiograms, vector loops were constructed on a rectangular coordinate system. These were later compared with photographs of the loops inscribed directly on the cathode-ray oscilloscope. The photographs of the loops recorded on the face of the cathode-ray screen were projected as individual frames and studied for contour and direction.

RESULTS

Inasmuch as the series of subjects was small, it was deemed advisable to divide the subjects into three groups according to the electrical "position" of the heart: (1) vertical and semivertical, (2) intermediate, and (3) semihorizontal and horizontal. There were fifteen subjects with vertical or semivertical hearts, four subjects with intermediate position of the heart, and six with semihorizontal or horizontal hearts. Results are tabulated in Tables I to V and illustrated in part in Figs. 1 and 2.

DISCUSSION

In the scalar headward-footward ballistocardiogram, the H wave occurred as an initial headward deflection, the origin of which has been controversial. Hamilton and co-workers[3] felt it was related to isometric contraction of the ventricles and the apical thrust. On the other hand, Nickerson and Curtis[2] contended that it was associated with auricular contraction. DeLalla and co-workers[11] associated it with the apex thrust and the auricular contraction wave

in the neck and skull. Starr[12] recently has taken the view that, although there was good evidence that the H wave may arise as a result of auricular activity, there were other factors in its genesis. He suggested that movements of blood in the heart during contraction of the chambers before ejection could produce an impact by changing the heart's center of mass. In a case of ventricular aneurysm Starr[12] found large H waves, while in other instances of ventricular aneurysm large H waves could not be demonstrated. In the latter cases he explained the absence of large H waves as due to the fact that the aneurysmal

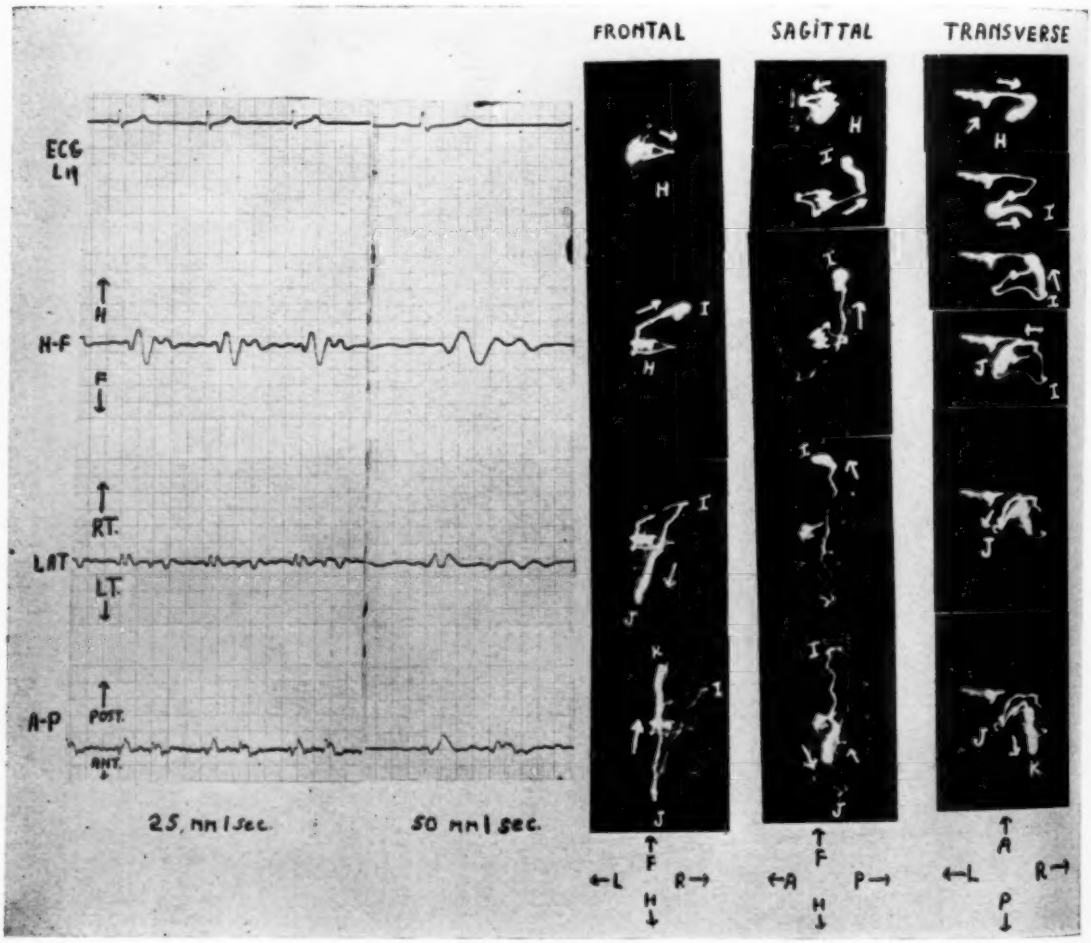

Fig. 1.—Subject E. T. Semivertical heart. Selected successive frames but not consecutive, illustrating the formation of the *H*, *I*, *J*, and *K* loops. The L loop is not depicted. The frames are read from the top to bottom. Right and left are the subjects' right and left. In the frontal plane the *H* loop is inscribed clockwise directed to the right, then left and headward. In the sagittal plane the *H* loop is inscribed counterclockwise and is directed anteriorly and headward. In the transverse plane the *H* loop is inscribed clockwise and directed to the left then anteriorly and finally to the right giving an ellipsoidal shape. The *I* loop is inscribed clockwise and directed footward and to the right in the frontal plane, counterclockwise footward and posteriorly in the sagittal projection, and counterclockwise, to the right and posteriorly in the transverse plane. The *J* loop in the frontal plane is inscribed counterclockwise and directed headward and to the left; clockwise, slightly anteriorly and headward in the sagittal projection; counterclockwise, to the left and slightly anteriorly, in the transverse plane.

bulge was so situated that motion of blood in it was not in the body's longitudinal direction and so would not be recorded by conventional techniques. In the normal subject, our observations on the genesis of the H wave and its relationship to body axis were somewhat in accord with the above observations of Starr.

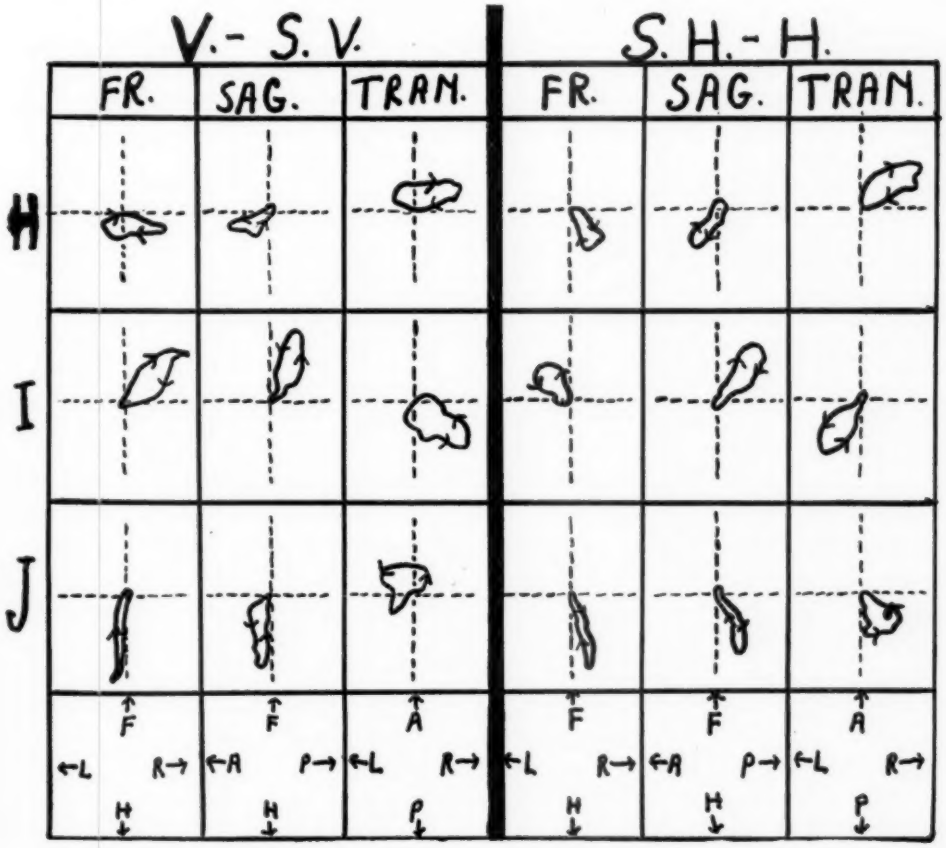

Fig. 2.—Idealized, diagrammatic loops reconstructed from multiple photographic frames, illustrating the spatial relationship of the vectorballistocardiogram and cardiac position. In the group of subjects having vertical and semivertical position of the heart, the *H* loop was directed headward, leftward and rightward and anteriorly, as compared with individuals who have horizontal and semihorizontal hearts where the *H* loop was directed headward, rightward and anteriorly. The *I* loop was directed footward, rightward and posteriorly in the vertical and semivertical group; in contrast, in the horizontal and semihorizontal group the *I* loop was directed footward, leftward and posteriorly. The *J* loop, in the vertical and semivertical group, was directed headward, leftward and slightly anteriorly; in comparison, in the horizontal and semihorizontal group the *J* loop was directed headward, rightward and posteriorly. There was no correlation between cardiac position and the direction of the *K* and *L* loops, and hence the *K* and *L* loops are not illustrated.

In a previous study[13] utilizing the electrokymograph as a timing device, we have been able to relate the H wave from onset to the peak with the period of isometric contraction of the ventricle. In the present study the spatial relationship of the H loop was well correlated with the anatomic position of the heart. In subjects with horizontal position of the heart the body motion which was represented by the H loop was directed definitely more headward, rightward, and anteriorly than in subjects with vertical position of the heart (Table I and Fig. 2).

The I wave of the scalar headward-footward ballistocardiogram represents cardiac recoil due to ejection of blood from the ventricles into the aorta and pulmonary arteries.[3,14] It occurs early during the rapid ejection phase of ventricular contraction.[13] Starr, and his colleagues[16] recognized that the depth of the I wave in the longitudinal axis was influenced by the cardiac-aortic axis in extreme cases. Jones and Goulder[17] using a low-frequency critically damped table also felt that there was a relationship between cardiac position and the ratio of H-I to J-K amplitude in the scalar headward-footward ballistocardiogram.

TABLE I. THE RELATIONSHIP OF THE H WAVE IN THE HEADWARD-FOOTWARD AXIS TO MOTION OF THE BODY IN THE LATERAL AND ANTEROPOSTERIOR AXES

NUMBER OF SUBJECTS	*V.-S.V. 15	†INTER. 4	‡S.H.-H. 6
Left	2	1	1
Right	2	2	3
Left and right	11	1	2
No lateral component	0	0	0
Anterior	9	2	3
Posterior	3	0	1
Anterior and posterior	1	1	2
No anteroposterior component	2	1	0

*Denotes subjects with vertical and semivertical position of the heart.
†Denotes subjects with intermediate position of the heart.
‡Denotes subjects with semihorizontal and horizontal position of the heart.

Hamilton and co-workers,[3] who early recorded the ballistocardiogram in three axes, described the wave as being directed footward, ventral, and to the left. However, position of the heart and the number of subjects studied were not stated. Scarborough and his associates[4] described the spatial direction of the I loop as footward, slightly to the right and anteriorly. Brandt and associates[7] observed that synchronous with the footward I wave in the longitudinal ballistocardiogram there was a significant leftward wave in 45 per cent and a rightward wave in 8 per cent of the lateral records. Braunstein[22] reported that the I loop represented a motion directed footward, right, and frontward. Our observations indicate a definite relation between the direction of body motion represented by the I loop and the anatomic position of the heart. In subjects with horizontal position of the heart the body motion which is represented by the I loop was directed predominantly to the left, and in subjects with vertical position of the heart predominantly to the right. In the latter, the direction was also more posterior (Table II and Fig. 2). This correlation of the I loop with cardiac position may reconcile the variable findings by other observers on the spatial direction of the I wave.

TABLE II. THE RELATIONSHIP OF THE I WAVE IN THE HEADWARD-FOOTWARD AXIS TO MOTION OF THE BODY IN THE LATERAL AND ANTEROPOSTERIOR AXES

NUMBER OF SUBJECTS	*V.-S.V. 15	†INTER. 4	‡S.H.-H. 6
Left	1	2	5
Right	12	2	1
Left and right	0	0	0
No lateral component	2	0	0
Anterior	1	2	2
Posterior	11	1	4
Anterior and posterior	0	0	0
No anteroposterior component	3	1	0

*Denotes subjects with vertical or semivertical position of the heart.

†Denotes subjects with intermediate position of the heart.

‡Denotes subjects with semihorizontal or horizontal position of the heart.

The J wave occurs at the end of the rapid-ejection phase of the ventricle and is usually ascribed to the deceleration of blood in the heart, ascending aorta and pulmonary artery, and to the acceleration of blood in the descending aorta.[3] In studies of others the J wave was found quite variable. Hamilton and associates[3] reported that it was directed headward, to the left, and ventral (anteriorly). Scarborough and associates[4] on the other hand, described the J wave as being directed headward, slightly to the left, and posteriorly. Franzblau and associates[5] using a critically damped table reported results similar to those of Scarborough and associates. Brandt and co-workers[7] found that the J wave was directed to the right or left, but in a greater number of instances directed toward the right. These workers felt that torsional change may explain the marked variability of results. However, from our findings, it appears that body build and position of the heart played an important role in the direction of body motion recorded.

Inasmuch as the J wave is primarily initiated by direct ventricular activity one would expect a change in the spatial relationship of the J loop with change in position of the heart. Such a correlation was quite striking in the subjects studied. In the subjects with vertical and semivertical hearts, we found the J loop in the frontal plane was directed headward and to the left, and in those with semihorizontal and horizontal hearts, it was directed headward and to the right. In the sagittal plane the J loop was directed headward and anteriorly in about one-half the subjects with vertical and semivertical hearts, and in the other one-half it was directed headward with no anteroposterior projection. In contrast to this, in the intermediate, semihorizontal, and horizontal groups, the J loop was directed headward and posteriorly (Table III and Fig. 2).

TABLE III. THE RELATIONSHIP OF THE J WAVE IN THE HEADWARD-FOOTWARD AXIS TO MOTION OF THE BODY IN THE LATERAL AND ANTEROPOSTERIOR AXES

NO. OF SUBJECTS	*V.-S.V. 15	†INTER. 4	‡S.H.-H. 6
Left	9	3	2
Right	3	1	4
Left and right	0	0	0
No lateral component	3	0	0
Anterior	6	1	1
Posterior	2	2	4
Anterior and posterior	0	0	0
No anteroposterior component	7	1	1

*Denotes subjects with vertical or semivertical position of the heart.
†Denotes subjects with intermediate position of heart.
‡Denotes subjects with semihorizontal or horizontal position of the heart.

The K and L vectors were essentially headward-footward and had little representation in the lateral and anteroposterior axis (Tables IV and V). This was not unexpected in view of the fact that these waves arise as a result of pulsatory phenomena of the descending aorta and its ramifications in the abdomen and extremities. Other observers[3,4,7] have similarly noted the predominantly headward-footward direction of the K and L waves.

TABLE IV. THE RELATIONSHIP OF THE K WAVE IN THE HEADWARD-FOOTWARD AXIS TO MOTION OF THE BODY IN THE LATERAL AND ANTEROPOSTERIOR AXES

NO. OF SUBJECTS	*V.-S.V. 15	†INTER. 4	‡S.H.-H. 6
Left	2	0	2
Right	9	1	4
Left and right	0	0	0
Anterior	3	2	1
Posterior	2	0	2
Anterior and posterior	0	0	0
No anteroposterior component	10	2	3

*Denotes subjects with vertical or semivertical position of the heart.
†Denotes subjects with intermediate position of the heart.
‡Denotes subjects with semihorizontal or horizontal position of the heart.

Scarborough and his co-workers[15] found the amplitude of waves in the lateral ballistocardiogram was greater than in the headward-footward with increasing age but felt that the progressive shift of the anatomic axis of the heart toward the horizontal position was not a factor. Contrary to this, Edson and associates[19] found that the variation in ballistic pattern of normal subjects was related to variations in cardiac position.

TABLE V. THE RELATIONSHIP OF THE L WAVE IN THE HEADWARD-FOOTWARD AXIS TO MOTION OF THE BODY IN THE LATERAL AND ANTEROPOSTERIOR AXES

NO. OF SUBJECTS	*V.-S.V. 15	†INTER. 4	‡S.H.-H. 6
Left	7	1	2
Right	4	2	1
Left and right	0	0	0
No lateral component	4	1	3
Anterior	0	0	1
Posterior	6	1	2
Anterior and posterior	0	0	0
No anteroposterior component	9	3	3

*Denotes subjects with vertical or semivertical position of the heart.
†Denotes subjects with intermediate position of the heart.
‡Denotes subjects with semihorizontal or horizontal position of the heart.

These findings on the spatial relationship of the various waves of the ballistocardiogram indicate the striking fact that the H, I, and J waves, arising as a direct result of ventricular contraction, have a definite spatial relation to cardiac position. In contrast to this the K and L waves, arising as a result of phenomena of peripheral circulatory action, have no significant spatial change due to position of the heart. Although the data presented revealed a definite correlation of the vectorballistocardiogram with cardiac position, there are probably additional factors involved in the explanation of the spatial relationship of the various waves of the ballistocardiogram. Consideration of individual elasticity of the body and its associated vibratory phenomena and cross modes of vibration together with torsional changes are other factors that require further investigation. Clarification of these points would be an aid in the better evaluation of the headward-footward ballistocardiogram.

SUMMARY

By means of a direct-body pickup utilizing a coil and magnet, the headward-footward, lateral, and anteroposterior movements of the body were simultaneously recorded with Lead I of the electrocardiogram on a four-channel direct-writing oscillograph. The vectorballistocardiogram was successively recorded in the

frontal, sagittal, and horizontal planes of the body by means of a cathode-ray oscilloscope. The spatial vectors corresponding to the H, I, and J waves of the ballistocardiogram were found to be related to the anatomic position of the heart; on the other hand, there was no correlation of the K and L vectors with cardiac position. The possible significance of vectorballistocardiography in relation to the usual method of longitudinal scalar recording of the ballistocardiogram was discussed.

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EXPERIMENTAL ECTOPIC CARDIAC RHYTHMS

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EXPERIMENTAL investigation of the ectopic rhythmic firing of impulses in the heart muscle has received relatively little attention as compared to the study of the same problem in various types of nerves. This may be due to the fact that in most experiments the various compounds were injected intravenously and therefore caused stimulation of many centers leading to irregular arrhythmias. For more than twenty years, the only pertinent experimental studies had been those in which the animal received small doses of barium chloride or strophanthin accompanied by faradic stimulation of the vagus and sympathetic nerves; irregularities of the ventricular rhythm appeared frequently, but their unifocal origin could not be controlled.[17] A fairly large area is also involved when ectopic arrhythmias appear following ligation of a coronary artery.[8,12]

In recent years, three new ways were described by means of which one can establish rhythmic firing of impulses in one center, that is, in one cell or a small group of cells. In one, a point of the ventricular surface is stimulated either mechanically or electrically after previous sensitization of the heart with barium and quinidine. In another, the heart is sensitized with a minute amount of aconitine, and the vagus is stimulated. This method elicited for the first time a regular bigeminal rhythm in which the extrasystoles were always of the same form as those seen in man. The third method is the topical application or subepicardial injection of various compounds such as sodium chloride, barium chloride, aconitine, digitalis, strophanthin, veratrine, and acetylcholine.[22]

In the present study ectopic rhythms elicited by focal injection of sodium chloride, veratrine, sodium oxalate, and sodium citrate are compared. The latter two compounds were used since there is ample evidence that in various types of nerve and in skeletal muscle topical application of these agents facilitates or elicits rhythmic firing of impulses by influencing the calcium content of the fibers. Aconitine was not employed this time since its effects were reported elsewhere,[22] and since ventricular fibrillation often follows its application to the ventricle of

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This investigation was supported (in part) by a research grant from the National Heart Institute, U. S. Public Health Service.

Received for publication April 12, 1954.

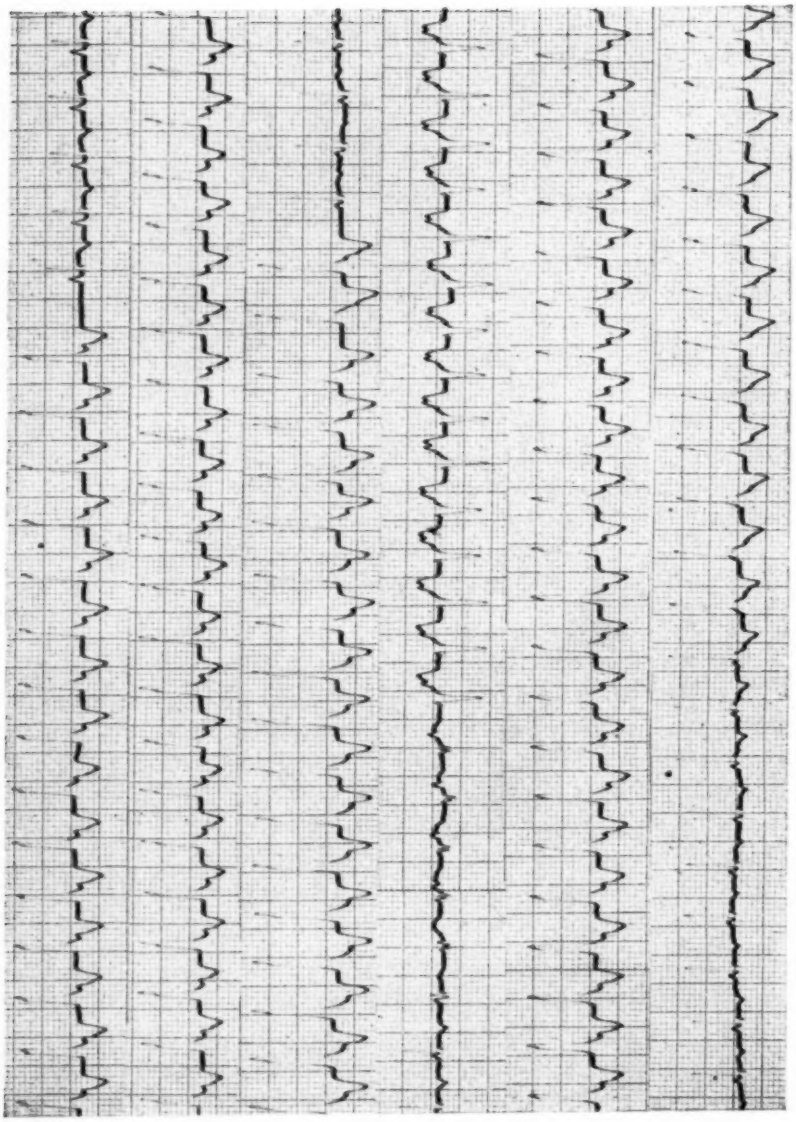

Fig. 1.—Experiment of March 31, 1953. *A* reveals a sinus rhythm with a rate of 150 at the end of the strip. Preceding the sinus rhythm there is an ectopic tachycardia elicited by injection of a 10 per cent solution of sodium chloride into the right ventricle: its rate varies from 166 at the beginning of the strip to 150 just before the conversion. The same rate (150-166) was noted when the tachycardia was elicited by injection of a 3.8 per cent solution of sodium citrate in a nearby area of the same ventricle (*B*) and into the conus of the right ventricle (*C*). *D* shows an ectopic tachycardia (rate 166-176) produced when a 3.8 per cent solution of sodium citrate was injected into the left ventricle. Veratrine injected twice into the right ventricle caused a tachycardia with the same rate, 166 (*E*, *F*).

right ventricle caused a tachycardia with the same rate, 166 (*E*, *F*).

Fig. 2.—Experiment of April 7, 1953. The sinus rhythm (rate of 187) is followed by a tachycardia of the same rate induced by an injection of 10 per cent sodium chloride into the right ventricle (*A*) while an injection of 1 per cent sodium citrate into the left ventricle caused a tachycardia with a rate of 200 (*B*). A 1 per cent solution of sodium citrate into the right ventricle produced a tachycardia of 187 per minute (*C*) which also appeared (*D*) when a 3.8 per cent solution of the same compound was used. Veratrine applied to the left ventricle caused a tachycardia of 176 (*E*).

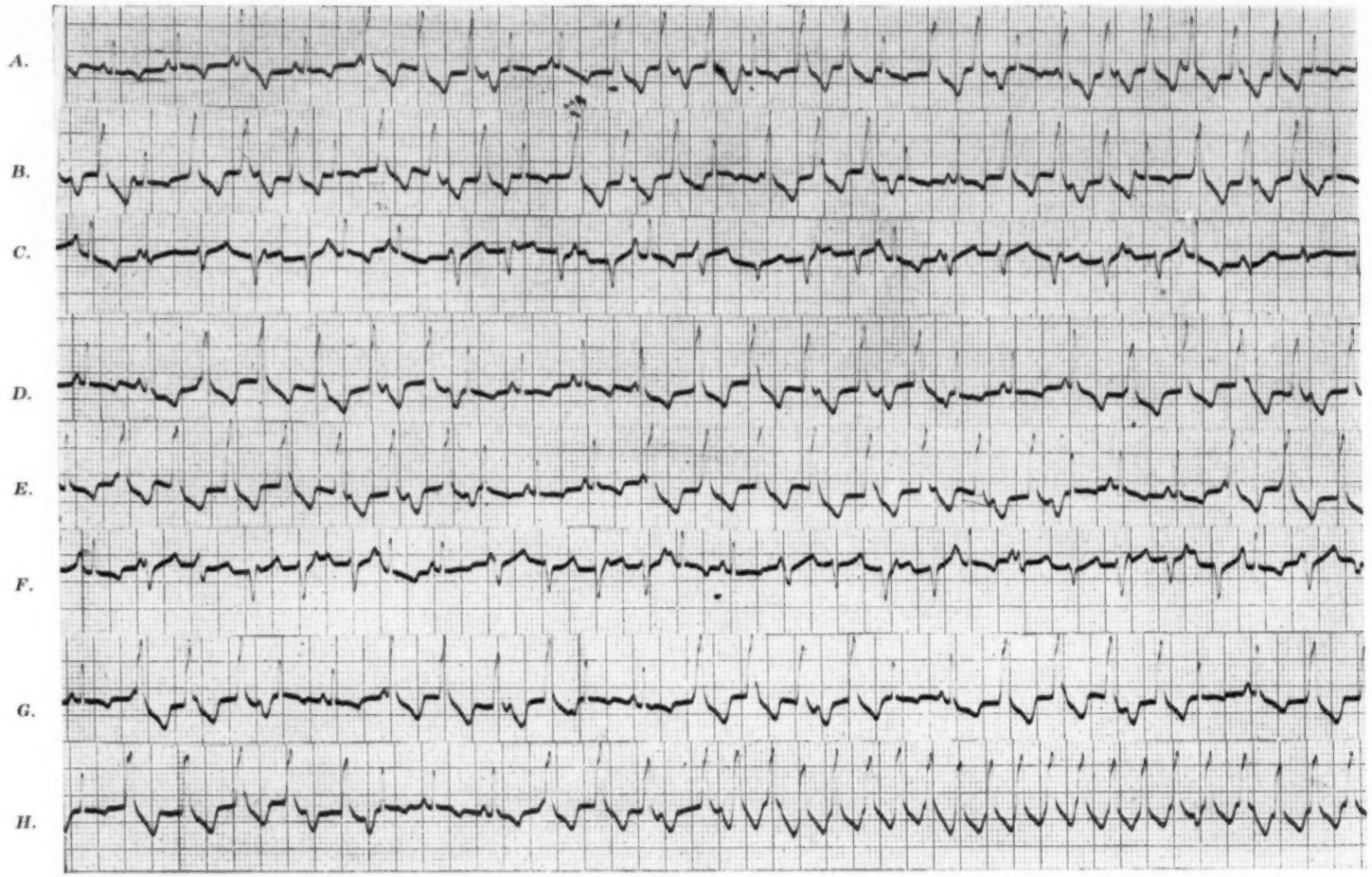

Fig. 3.—Experiment of April 14, 1953. *A* shows a sinus rate of 130 and a series of ectopic beats, elicited by applying a 10 per cent solution of sodium chloride; the rates varied from 150 to 176. A solution of 3.8 per cent of sodium citrate was applied to the right ventricle (*B*) and to the left ventricle (*C*) and elicited a series of ectopic beats with a rate of 157. A 1 per cent solution of sodium oxalate injected into the right ventricle produced abnormal beats with a rate of 150 (*D*). Veratrine injected into the right ventricle (*E*) and in the left ventricle (*F*) induced ectopic beats with a rate of 150-157. Moreover, ectopic beats with a rate of 150 were caused by veratrine injected into the right ventricle (*G*). On warming the area of application (*H*) the rate immediately rose to 250. In these tracings the ectopic beats were not conducted back to the auricles and the P waves of the sinus rhythm are visible in the ectopic beats.

the dog. Barium chloride and digitalis were not used because they elicit irregular ectopic rhythms which therefore cannot be compared with the regular ones appearing after the other compounds.

METHOD

In all the experiments the dogs were anesthetized with an intraperitoneal injection of Nembutal; the dose was 1 c.c. per 3 kg. After artificial respiration had been instituted, the heart was exposed by removing the sternum and the adjacent portions of the ribs, and the pericardium was opened. Both vagi were severed in the neck, and the electrocardiogram was registered in Lead I unless otherwise stated. All substances used (sodium chloride, sodium oxalate, sodium citrate, and veratrine) were injected subepicardially in the amount of 0.05 c.c. with a tuberculin syringe. They were injected in different parts of the right ventricle or in the apical area of the left ventricle. Sodium chloride was used as a 5 or 10 per cent solution; sodium oxalate and sodium citrate as a 1 per cent or 3.8 per cent solution; veratrine as a freshly prepared 0.05 per cent solution. No substance was injected until the effects of the previously administered substance had completely subsided. In no experiment were all substances used. This was done in order to prevent one compound from influencing the action of the other. They were used in different combinations. Cooling or warming was done with thermodes filled with ice water or with water heated to 50° C.

RESULTS

In twenty-two of twenty-nine experiments, the injection of the compounds mentioned previously caused rhythmic firing of impulses. Of the seven negative results, two occurred in dogs ill with pneumonia, two dogs had inadvertently been given an excessive dose of Nembutal, and three exhibited anoxia with cyanosis which could not be abolished.

Figs. 1 to 10 reveal the constant form of the ectopic rhythm when it originated in the same focus. There are, of course, the anticipated differences of form as the foci of origin varied; thus, it is evident that an ectopic beat originating from the conus of the right ventricle just beneath the pulmonary valves will have a different ventricular complex than one originating near the apex of the right ventricle. Whenever ectopic beats appeared following the injection of any of these compounds into a given area, their form remained the same. Slight variations of the ectopic periods (distance between two consecutive ectopic beats) were common, in addition to the appearance of the firing of impulses in groups, which will be discussed later. As is commonly seen in any type of rapid impulse formation, for example postfaradization flutter, an alternation of the duration of the period is often present. There were variations of the successive periods up to 0.06 sec., but they were rarely that marked. Their appearance was most frequent after sodium citrate or sodium oxalate injections and was rare after veratrine.

Occasionally, the ectopic rate slowed before the ectopic beats disappeared; however, they often disappeared with no change in rate. The latter was the case in those instances in which the ectopic ventricular beats were not reversely con-

with a rate of 150 (*D*). Veratrine injected into the right ventricle (*E*) and in the left ventricle (*F*) induced ectopic beats with a rate of 150-157. Moreover, ectopic beats with a rate of 150 were caused by veratrine injected into the right ventricle (*G*). On warming the area of application (*H*) the rate immediately rose to 250. In these tracings the ectopic beats were not conducted back to the auricles and the P waves of the sinus rhythm are visible in the ectopic beats.

ducted to the auricle; thus, the sinus rhythm could proceed without disturbance in that chamber, and after a variable number of ectopic beats the sinus rhythm again became dominant. As is seen in Fig. 3, after injection of various substances, there was interference of the sinus rhythm with the ventricular rhythm, each one controlling the ventricles for a few beats, alternately. When the ventricular ectopic beats were conducted back to the auricles, long chains of uninterrupted ectopic beats occurred having the appearance of a paroxysmal ventricular tachycardia. Since the propensity to reverse conduction of the ventricular ectopic beats varies with the animal, it is understandable that in those animals in which this characteristic was absent, all compounds caused interference as in Fig. 3, whereas in others having this characteristic, long chains of ectopic beats are seen, as in Figs. 1 and 2. After their disappearance, inhibition of the sinus rhythm by faradic stimulation of one of the vagi in the neck caused these ectopic beats to reappear at a somewhat slower rate.

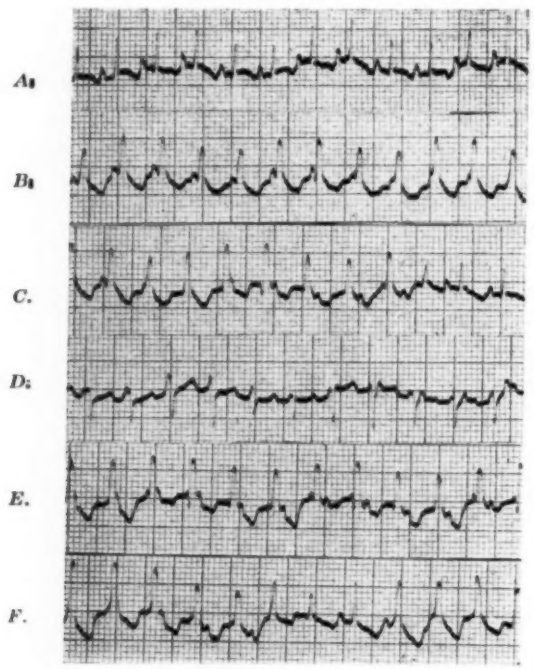

Fig. 4.—Experiment of Oct. 13, 1953. A sinus tachycardia (rate of 214) existed (*A*). Application of a 5 per cent solution of sodium chloride caused a tachycardia with a rate vraying between 214 and 230 (*B*); another tachycardia was elicited by a 10 per cent solution of sodium chloride (*C*) and had a rate of 214. Application of the same substance to the left ventricle (*D*) again caused a tachycardia of 214. With the application of a 3.8 per cent solution of sodium citrate and later of veratrine on the right ventricle (*E*, *F*) the ectopic rates remained 214.

It is interesting to note the similarity between the rates of the ectopic rhythms and of the sinus rhythm, and therefore between the ectopic rhythms themselves. This is shown in Table I and in Fig. 1 to Fig. 8 where with faster sinus rates faster ectopic rates appeared, and vice versa. Thus the fastest ectopic rate of 230 (Fig. 4) was seen with a sinus rate of 214, while the slowest rate of 125 appeared with a sinus rate of 128.

TABLE I. DURATION OF DIASTOLE (R-R INTERVAL) OF SINUS AND ECTOPIC RHYTHMS OF RIGHT (R) OR LEFT (L) VENTRICLES (HUNDREDTHS OF A SECOND)

NO.	DATE	SINUS RHYTHM	VERATRINE	Na OXALATE (1%)	Na OXALATE (3.8%)	Na CITRATE (1%)	Na CITRATE (3.8%)	NaCl (5%)	NaCl (10%)
1	6- 7-52	32	32	28-32					36
2	1-13-53	38 40	34 36	R.36 L.36 38		40	38		40
3	1-27-53	44-48	44			44			
4	2-10-53	36	36		36				30
5	3- 3-53	36	36						34
6	3-10-53	44	38-40	40	40				40
7	3-17-53	33	R.33 L.33	28			R.30 L.33		28
8	3-24-53	28-36	36			36	36	36	
9	3-31-53	30-40	36-42		38-40	38	R.36 L.36		38 40
10	4- 7-53	32	R.34 L.34			R.32 L.32	32		R.32 L.32
11	4-14-53	40-46	R.40 L.40	40		32	R.44 L.44		40
12	4-21-53	36		36			38		36
13	4-28-53 4-28-53 4-28-53	44 46 48	R.42 L.42 40 44-48	42			44 R.40 L.40	40 40	44 44 44-48
14	5- 5-53	39	36				36	36	34
15	5-19-53	40	40	36		40	38-40		36
16	5-26-53	46	44	40		44	44	44	44
17	6- 9-53	40?	30				32	32	32
18	6-16-53	30-42	40	40	32		40	30	30
19	10-13-53	28	28		28		28	26-28	R.28 L.28
20	10-27-53	40	36-40		36-44		36-42		36-40
21	11-11-53	36	36				36	36	32
22	12-30-53	40				40		40	40

Of course, variations and exceptions to this rule were observed and they are understandable, as ectopic firing of impulses depends on many factors. However, the similarity between the rates of the ectopic rhythms elicited from different foci both with the same compound and with different compounds is evident. Slight variations did occur between successive beats as mentioned previously. It is clear that when the rate is rapid, variations of only a few hundredths of a second between successive beats expressed in rate per minute represent a marked absolute difference, whereas this difference expressed in percentage is small. The figures illustrate the similarity in the rate of these rhythms. When there were marked variations of diastole between two successive ectopic beats after injection of one of the compounds, the same phenomenon was present after injection of each of the other compounds (Fig. 9).

If the rate of the ectopic rhythm were markedly slower than that of the sinus rhythm it could not have become manifest since the faster rhythm suppresses the slower one. Vagal stimulation revealed, however, the rarity of slow ectopic rhythm.

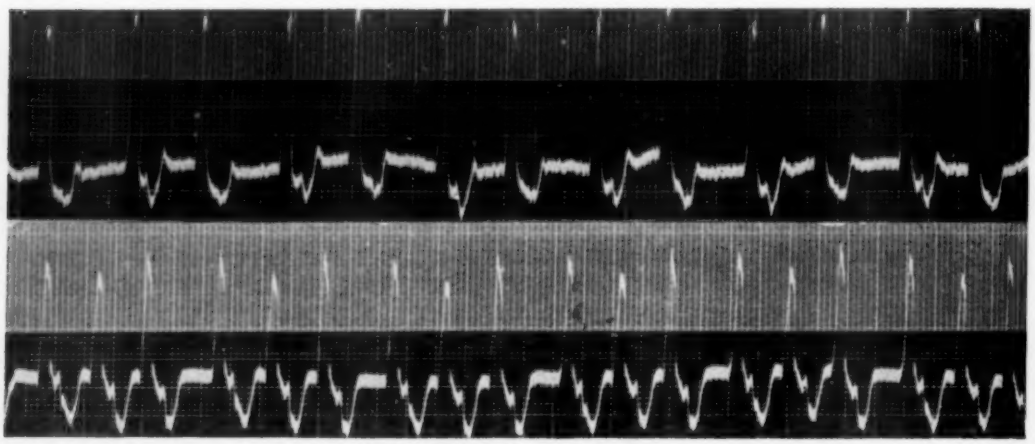

Fig. 5.—These tracings were obtained in different experiments after application of veratrine on the right ventricle and show ectopic beats in groups.

The rate of the ectopic rhythms was independent of the concentration of the agent. As shown in Figs. 2 and 4 and in Table I, the rate remained the same whether we used a 5 or 10 per cent solution of sodium chloride or a 1 or 3.8 per cent solution of sodium citrate or oxalate.

All ectopic rhythms appeared within one minute. The longest latent period was observed with veratrine. The rhythms lasted from a few seconds to 4.3 minutes, the longest being caused by veratrine. When during an experiment there was a change in the rate of the sinus rhythm, a parallel change was often observed in the ectopic rhythm.

The rarity of the appearance of a bigeminal rhythm was astonishing. The rare occurrence of this disturbance of rhythm has been stressed previously. While we did see it after sodium chloride, it was never seen to follow sodium oxalate or citrate (Fig. 6).

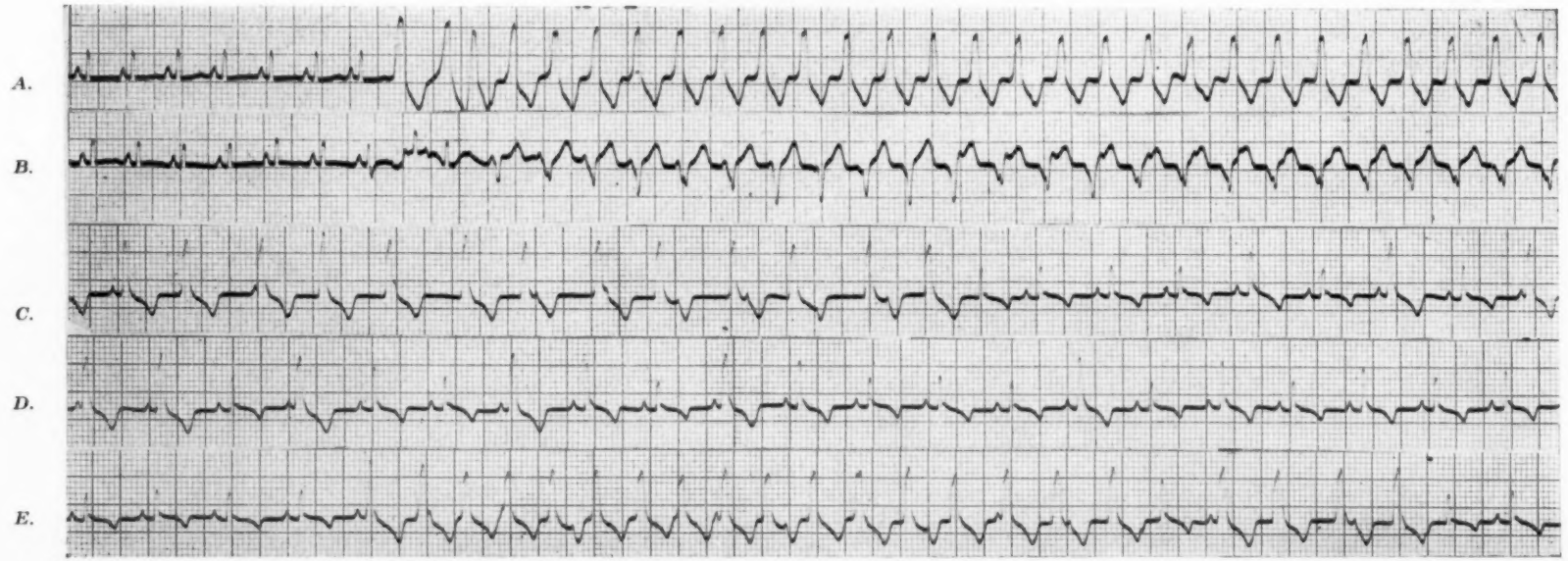

Fig. 6.—*A* and *B* were obtained from the same experiment as Fig. 2. The tachycardias provoked by injections of veratrine in both ventricles had subsided. Mechanical stimulation of an injected area in the right ventricle (*A*) and the left ventricle (*B*) reinduced the respective tachycardias, both at a rate of 187. *C* is from the experiment of April 28, 1953. Application of a 10 per cent solution of sodium chloride on the right ventricle caused ectopic beats in groups with a slow rate. The rate of the sinus beats was 150. In *D* some ectopic beats appear so late in diastole that they are preceded by a P wave from the sinus node, simulating pre-excitation beats. Mechanical stimulation of the area of application of sodium chloride (*E*) caused a short burst of ectopic beats with a faster rate, which quickly subsided.

Occasionally groups of ectopic beats appeared (Figs. 5 and 6). Such groups usually consisted of two beats, seldom three, and persisted for the duration of the abnormal rhythm. In some experiments the tendency to form stimuli in groups was greater than in others. When such a tendency existed, it became evident after the injection of any of the compounds. A regular ectopic rhythm changed for no known reason into ectopic beats in groups, and vice versa. The ectopic beats in groups appeared particularly when there was reverse conduction to the auricles.

When the rate of the ectopic beats was identical with that of the sinus rate and there was no reverse conduction, and therefore no disturbance in sinus activity, it happened frequently that a series of abnormal ventricular complexes was fortuitously preceded by a normal P wave, with a short P-R interval, imitating the pattern seen in the pre-excitation syndrome (Fig. 7).

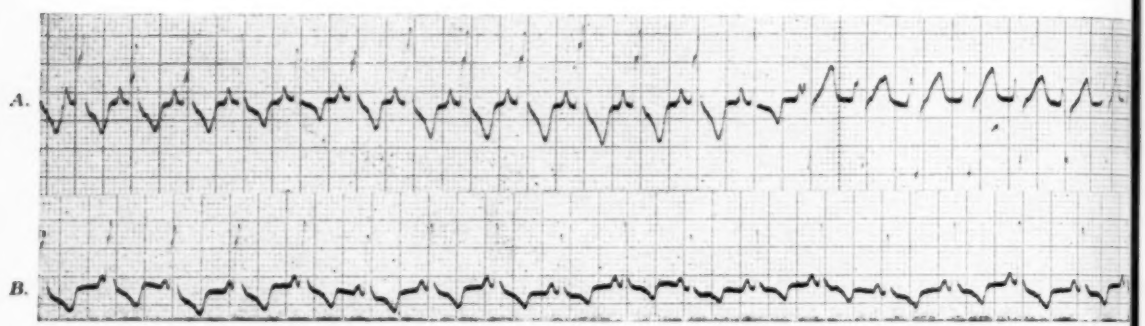

Fig. 7.—In the experiments of March 3, 1953, and April 14, 1953, (*A* and *B*, respectively), veratrine was applied on the right ventricle. Since the ectopic rate and that of the sinus rhythm are similar, interferences appear in which the P wave precedes the ectopic beat at a shortened distance thereby simulating the picture of a pre-excitation syndrome.

Mechanical stimulation by striking the area of injection of the compound with a blunt instrument often induced or reinduced the arrhythmia, but only when performed within a short time after it had disappeared. This is especially true after veratrine, whose long latent period is markedly shortened in this manner. Upon striking the area, the ectopic rhythm accelerated but quickly reverted to the same rate as caused by the injection of the compound alone (Fig. 6). In the presence of a regular trigeminal rhythm, the rate of the ectopic beats occasionally increased for about one minute (Fig. 8).

It was the rule that the similarity of rate between various rhythms was independent of the ventricle used (Figs. 1, 2, 6, and 10). Injection of the different compounds into the right or left ventricles elicited ectopic rhythms with the same rate. Any of these trains of ectopic beats could be abolished immediately by injection of a 1 per cent solution of potassium chloride into the area which had received the substance provoking the ectopic beats.

Cooling slowed the rate and always abolished the existing ectopic rhythm (Fig. 9), while warming of this area accelerated an existing ectopic rhythm or reinduced one which had previously stopped. This proves that the ectopic rhythm actually originated in the treated area (Fig. 3).

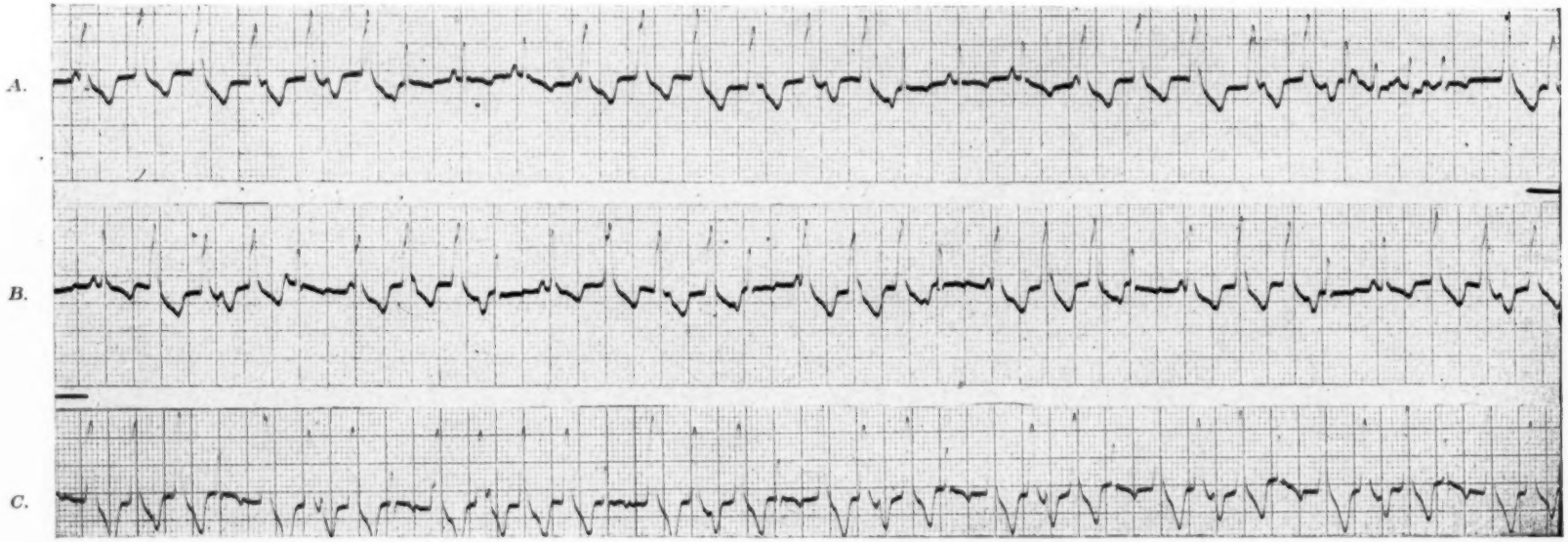

Fig. 8.—Experiment of April 14, 1953. *A* shows groups of ectopic beats which appeared after veratrine. The sinus rate is 140, and the rate of the ectopic rhythm is 150. At the end of *A* the area of application of veratrine was stimulated mechanically and the ectopic rate increased to 166 (*B*). *C* is from another experiment: as a consequence of application of 10 per cent sodium chloride there is a quadrigeminal rhythm and one run of four extra beats following one sinus beat.

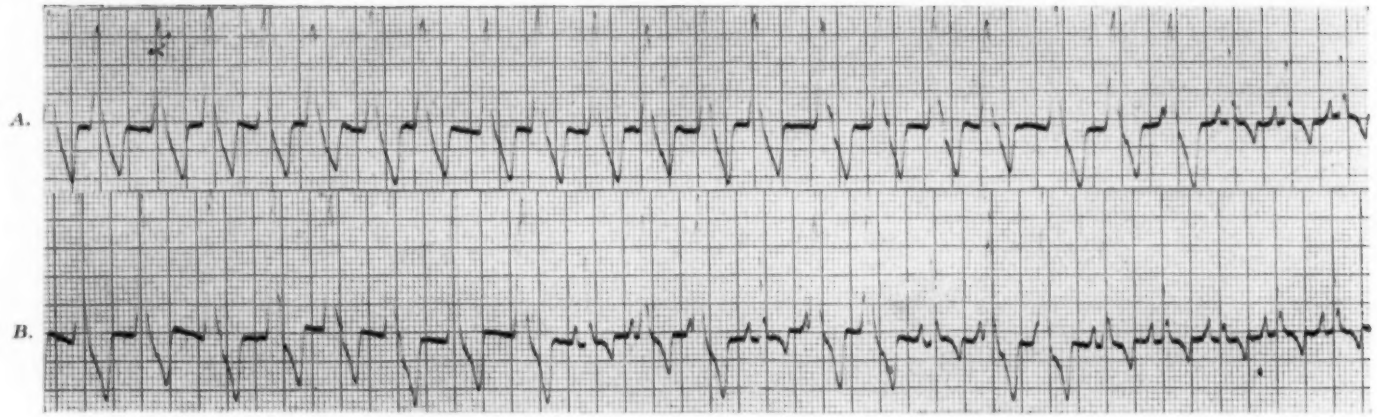

Fig. 9.—Shows ectopic beats after application of a 10 per cent solution of sodium chloride (*A*), and after veratrine (*B*). In both experiments the extra beats were abolished immediately by cooling the area of application of these substances. Before cooling, the ectopic rhythm was irregular.

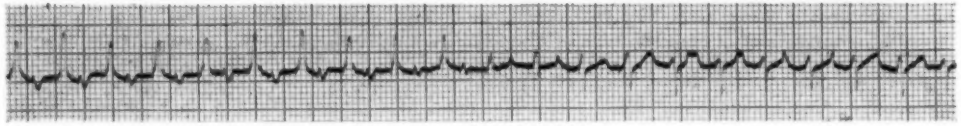

Fig. 10.—Experiment of Jan. 5, 1954. In this experiment veratrine was applied within a few seconds to the right and left ventricles. A right ventricular ectopic tachycardia with a rate of 176 is followed by one originating in the left ventricle with the same rate.

DISCUSSION

These experiments demonstrate that focal injection of sodium chloride, citrate, and oxalate as well as of veratrine in the aforementioned concentrations on the dog's ventricles is followed by a brief period of rhythmic firing of impulses. Although different substances were used, the rates of the ectopic rhythms thus created were approximately equal; exceptions do occur, and we are unable to explain them. Furthermore, the ectopic rate is usually slightly faster but occasionally equal to that of the existing sinus rhythm. The rate was independent of both the substance used and the area injected; this holds true for different areas of the same or the other ventricle. After the ectopic rhythm had vanished it could be re-elicited by a mechanical stimulus applied to the area of injection. This led to an initial acceleration of the ectopic rhythm which rapidly reverted to its former rate.

All the compounds used in these experiments elicited the same arrhythmic pattern in the different animals. It was manifested in some by long chains of ectopic beats, and in others by short groups of ectopic beats followed by one or more sinus beats. Both of these forms were caused by long trains of rhythmic impulses. These different patterns depended on the ability of the individual heart to conduct ectopic ventricular beats back to the auricles. When this was the case, the sinus rhythm could not interfere and a long chain of ectopic beats appeared. When there was no reverse conduction and therefore the ectopic beats were restricted to the ventricles, the formation of impulses from the sinus node could proceed undisturbed, and occasionally one or several sinus beats succeeded in reaching the ventricles and thus interfered with the ectopic rhythm.

Because of the similarity between the rates of the ectopic center and that of the sinus node, and because of the prevailing high rates it was not possible to say with certainty whether the ectopic center was always protected from the sinus beat, in other words whether parasystolic stimulus formation existed. In many instances, particularly with veratrine, this was the case.

The parallelism between the ectopic rates as created in these experiments and the sinus rhythm seems to be a quality common in the mammalian heart. In experiments in which ectopic rhythms were elicited in a different manner during an existing A-V rhythm,[18] or sinus rhythm, this similarity of rates of both rhythms was clearly evident.[15] This similarity has also been established with veratrine[20] and in specific tissue where four separate rhythms elicited in strands of "Purkinje fibers" had approximately the same rate.[23]

In some of our experiments the identical rates of the sinus and ectopic rhythms led to a picture simulating the pre-excitation syndrome. Similar pictures were created in the course of cardiac catheterization due to mechanical stimulation, and also during animal experiments, and often were misinterpreted as representing this syndrome.[22]

The results obtained in these experiments and summarized above suggest that an identical mechanism is created by the injection of the different substances and therefore leads to the formation of ectopic impulses having the same rate. Investigations on the so-called local potentials and prepotentials which may be

regarded as the basic phenomenon of impulse formation bring some support to this assumption. Brink and associates[5] state that the rhythmic excitatory process in the giant axon of the squid is of a fairly constant frequency, and Bozler found that in the depressed cardiac muscle oscillatory prepotentials have an intrinsic rhythmicity. These oscillations may be slowed by application of potassium or by cooling, and may be made more rapid by warming, but quickly return to their former rate after removal of these factors. One may assume that the ectopic centers in the same heart, regardless of location, have an intrinsic rate of oscillation dependent on many factors such as the enzyme system, electrolyte balance, and rate of metabolism of the cells. Thus, just as nerve fibers have their own rhythm of oscillation (Eigenrhythmus),[6] similarly, muscle may respond to different stimuli with a rate of oscillation characteristic for its fibers. One would have expected that the rhythmic impulse formation due to a chemical substance would depend solely on the properties and the concentration of this substance.

The intrinsic rate may be double that which is evident from the rate of the ectopic rhythm as the heart muscle may respond only to every second stimulus. A 2:1 response is often seen in nerves, and its existence may be surmised in muscle. It was noted in heart muscle of the turtle by Bozler[4] and was thought to exist in the dog's heart.[18]

The experiments in which sodium chloride were employed bring to mind important studies on nerve-muscle preparations.[14] When a crystal of sodium chloride was placed on the nerve of a nerve-gastrocnemius preparation and a single stimulus was applied to the nerve area thus altered, tetany of the muscle resulted from rapid regular stimuli formed in the altered area.

The effect of veratrine on the formation of rhythmic stimuli has been previously analyzed.[20] The action of sodium oxalate and sodium citrate on the heart has received little attention, although it plays a great role in neurophysiology. The application of these substances is a classical method of eliciting rhythmic impulse formation. Their effect is usually attributed to the removal of ionized calcium. Whether this be the case or whether the enzymatic formation of acetylcholine be diminished by sodium citrate[7] or the membrane potential be lowered,[13] sodium oxalate and sodium citrate elicit repetitiveness in a great many preparations (crustacean nerves, end plates, and mammalian nerves.[3,5,9,11]

The appearance of grouped ectopic beats is common in nerve physiology. Adrian has stressed this in particular. It was seen in single fibers of crustacean nerves following the application of sodium citrate by Arvanitaki,[3] and by Brink and associates in the nerve of the squid.[5] Adrian and Gelfan[2] found it in the decalcified frog muscle, and Pumphrey[16] in the sensory nerve of the frog following treatment with hypertonic solutions of sodium chloride in concentrations up to 18 per cent.

Consequently, this group response is a basic type of rhythm seen in different excitable tissues under varied conditions. Some experiments seem to show that this irregular response is due to occasional failure of the uninterrupted rhythmic oscillations to elicit a response, others believe that an impulse is not formed.[5]

The fact that grouped ectopic beats are seen not only in mammalian hearts including that of man[21] but are also present in single nerve and muscle fibers has practical importance because such group formations have been attributed in ectopic tachycardias to the existence of circus movements using alternating pathways of different lengths. Since circus movement is impossible in single nerves, it may safely be assumed that in the heart muscle the same mechanism, i.e., the firing of ectopic stimuli, is responsible during ectopic tachycardias.

The effect of warming or cooling the treated area, as well as the rate of the ectopic rhythms, also speaks against a circus movement in these experiments. As Lewis pointed out in regard to other types of tachycardias, if a circus movement were present the rate of the ectopic tachycardia should be much faster, owing to the speed of conduction in the ventricles.

The substances used in these experiments can lead to ectopic stimulus formation by causing oscillatory local potentials, which are propagated on attaining a certain height of negativity. It is also possible that they do not reach this height independently, but whenever a stimulus reaches the treated area it causes oscillatory after-potentials having a similar effect (pseudo-reflex action of Arvanitaki).

In these experiments it is most likely that the ectopic rhythms are not a consequence of injury. This was appreciated by Langendorff[10] when he studied the effects on ectopic rhythms following topical administration of different substances on the heart. It is further demonstrated by the differences noted after the use of barium or strophanthin, which cause irregular firing of impulses, or aconitine which causes much more rapid tachycardias, or potassium, which abolishes existing rhythms and does not elicit them, although it causes much more depolarization than any of the other agents used. Burning and mechanical injury of the cardiac surface lead to one or several ectopic beats, but they never lead to long chains as described in the present study. In addition, and supporting the conclusion that injury is not responsible, is the long latent period between the injection of veratrine and the appearance of the ectopic beats, while with sodium chloride, sodium citrate, and sodium oxalate, they appear within a few seconds.

SUMMARY

Sodium chloride, sodium oxalate, sodium citrate, and veratrine in various concentrations were injected subepicardially into the exposed heart of the dog. In twenty-two of twenty-nine experiments these substances elicited transient ectopic rhythms. The rate of these rhythms showed a constant relationship to that of the sinus rhythm and therefore a constant relationship among themselves; this relationship was independent of the concentration of the substances used as well as the area of injection in the right or left ventricle.

Certain forms of these ectopic rhythms depended on whether the ectopic ventricular beats were reversely conducted back to the atria.

Firing of ectopic beats in groups was observed, and the propensity of different hearts to this form of impulse formation was pronounced in some animals and absent in others.

The similarity between the rates of the prevailing sinus rhythm and the ectopic rhythm produced electrocardiographic tracings simulating the pre-excitation syndrome.

An attempt is made to explain the mechanism of these rhythms on the basis of data obtained in neurophysiology and skeletal muscle physiology.

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THE AXOSTAT

I. A New Instrument for the Multiaxial Registration of Extremity Electrocardiograms

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THE axostat, a new electrocardiographic instrument recently developed in this laboratory, produces any desired number of interpolated leads between the conventional bipolar extremity leads. The instrument consists basically of a three-phase voltage-dividing resistance network and an accurately calibrated battery-operated preamplifier. The resistance network (Figs. 1 and 3) consists of a balanced Y within an inverted balanced delta. A sliding contact can be adjusted to any desired position on the periphery of the network. Both arms and the left leg of the subject are connected by low-resistance (400 to 500 ohms) skin electrodes to the corresponding terminals of the resistance network. Potential differences between the center of the network and the sliding contact, after a predetermined amount of compensating amplification, are recorded by coupling the output of the instrument to an electronic electrocardiograph.*

THEORETICAL CONSIDERATIONS

The physical significance of axostat leads can probably be best appreciated by applying the concept of lead vectors to the instrument. These physical entities, first introduced into the electrocardiographic literature by Burger and van Milaan,[1,2] are such that the magnitude of a given lead may be expressed as the dot (or scalar) product of two vectors. One of these vectors represents the electromotive forces of the heart. The other vector, known as the lead vector, is a physical characterization of the given lead connection in the area where the electromotive forces arise. In a previous communication[3] we demonstrated that the lead vector is identical with the gradient of the electrical field which is generated when the lead pathway is reciprocally energized with one unit of current. It was also shown by applying the principle of superposition[3] that lead vectors exist not only for bipolar leads but also for certain types of synthetic leads such as the unipolar leads of Wilson and associates[4] and Goldberger.[5]

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Supported by grants from the National Heart Institute, United States Public Health Service, and from the Memphis Heart Association.

Received for publication Feb. 24, 1954.

*Model EK-2, The Burdick Corporation, Milton, Wis.

The idea of lead vectors may be readily extended to include axostat leads by means of the following development. In Fig. 1 the sliding contact is situated at the point P on the FL limb of the network periphery. The resistance between P and L may be expressed as nR, where n is a proportionality constant. The resistance between P and F will then be (1 − n)R. Then, by the principles of a voltage-dividing resistor,

$$E_P = (1 - n)E_L + nE_F \qquad (1)$$

where E_P, E_F and E_L are the potentials at the points P, F, and L, respectively. Subtracting E_C, the potential at point C, from both sides of the equation yields

$$E_{X'} = (1 - n)(E_L - E_C) + n(E_F - E_C) \qquad (2)$$

where $E_{X'}$ is the potential difference between points P and C. But the potential differences expressed in the parentheses of Equation 2 are identical to the Wilson and associates'[4] Leads V_l and V_f, respectively. Therefore

$$E_{X'} = (1 - n)\ V_l + nV_f \quad . \qquad (3)$$

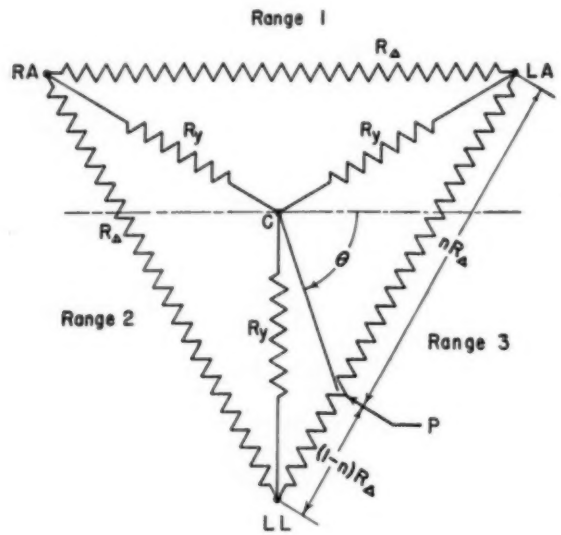

Fig. 1.—Voltage-dividing resistance network of the axostat. The terminals are represented as forming the apices of an equilateral triangle and the peripheral members are assumed to be linear resistors. The terminals *RA*, *LA*, and *LL* are connected to the right arm, left arm, and left leg, respectively. The proportionality factor, *n*, ranges in value from 0 to 1 depending upon the position of the sliding contact. Typical values of the resistors are R_Δ = 72,000 ohms, R_Y = 65,000 ohms.

If we assume that a lead vector, $\mathbf{L}_{X'}$, is associated with the lead connection P − C, then $E_{X'} = \mathbf{L}_{X'} \cdot \mathbf{F}_m$, where $\mathbf{F}_m$ is the vectorial expression of the electromotive forces of the heart. Also $V_l = \mathbf{L}_{Vl} \cdot \mathbf{F}_m$ and $V_f = \mathbf{L}_{Vf} \cdot \mathbf{E}_m$, where $\mathbf{L}_{Vf}$ and $\mathbf{L}_{Vl}$ are the vectors of the respective Wilson unipolar extremity leads. Substituting in Equation 3 yields

$$\mathbf{L}_{X'} \cdot \mathbf{F}_m = (1 - n)\ \mathbf{L}_{Vl} \cdot \mathbf{E}_m + n\mathbf{L}_{Vf} \cdot \mathbf{E}_m \quad . \qquad (4)$$

Factoring out the $\mathbf{E}_m$,

$$\mathbf{L}_{X'} = (1 - n)\ \mathbf{L}_{Vl} + n\mathbf{L}_{Vf} \quad . \qquad (5)$$

This relationship indicates that a lead vector consisting of 1 − n parts of the Lead Vl vector and n parts of the Lead Vf vector is associated with the lead connection P − C.*

The physical significance of the lead vector, $\mathbf{L}_X'$ is demonstrated in Fig. 2, *A*. The lead vectors of Vl and Vf are plotted as arising from the same origin, and the tips of the vectors are joined with a straight line of length *d*. A point is determined on this connecting line such that its distance from the tip of the Vl vector is nd [or (1 − n) d from the tip of the Vf vector]. A vector directed from the origin to this point constitutes a graphic representation of $\mathbf{L}_X'$. Similar relationships may be derived when the sliding contact lies between the points R and F, or between R and L. These relationships lead to the conclusion that the lead

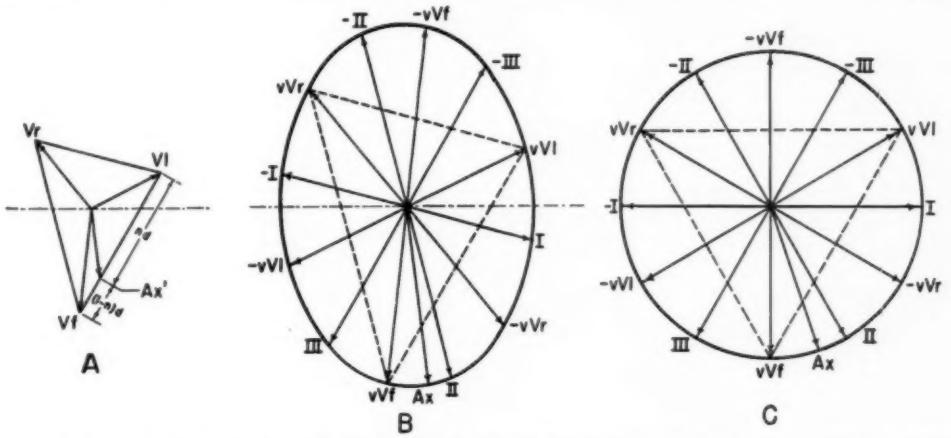

Fig. 2.—Illustration of the variety of lead vectors which is obtained with the axostat. *A*, Lead vectors obtained directly from the voltage-dividing network without preamplification, when the instrument is connected to a subject having the hypothetical Burger triangle shown in the figure. The lead vectors are represented as arising from the center (point where the medians intersect) of the triangle; the locus of the lead vector tips is the periphery of the triangle. The proportionality factor, *n*, is identical to that shown in Fig. 1; *d* is the length of the side of the triangle. The lead vector, *Ax'*, is that which would be obtained for the network setting shown in Fig. 1. *B*, Lead vectors for the same subject after the output voltage of the resistance network has been subjected to the preamplification described in the text. The lead vectors arise from the center of the figure and terminate in its elliptical periphery. Note that amplification of the network potentials does not alter the direction of the lead vectors. *C*, Lead vectors based on the assumption of an equilateral (Einthoven) triangular frame of reference. In both *B* and *C* the lead vector, *Ax*, corresponds to the network setting shown in Fig. 1.

vector, $\mathbf{L}_X'$, may be represented as a vector originating at the center of the Burger triangle (the point at which the medians intersect), with the periphery of the triangle constituting the locus of the vector tip. From these considerations it is apparent that the point P may be adjusted to particular positions on the periphery of the network which will produce any desired orientation of the associated lead vector in the plane of the Burger triangle.

Unamplified axostat leads, then, may be considered as projections of the spatial vectorcardiogram on any desired axis of the Burger triangle. The sensi-

*In a more rigorous type of analysis we concerned ourselves with the distribution of current which resulted when the network was reciprocally energized by an electromotive force applied to the points P and C. Assuming the resistance of the skin electrodes and the body to be negligible, we determined that ⅔ − n parts of the reciprocal current flowed through the Lead I pathway and ⅓ − n parts through the Lead III pathway. This result can be anticipated from Equation 5, thus tending to support thevalidity of the equation.

tivity of registration, however, is variable since the magnitude of the lead not only depends on the magnitude and relative direction of the electromotive force of the heart but is also directly proportional to the length of the lead vector.

Some attempt to compensate for these differences in sensitivity is made by amplifying the potential differences between P and C by a factor of $\sqrt{3/(1-3n+3n^2)}$ in the preamplifier section of the instrument. This procedure tends to equalize the lengths of the lead vectors as the peripheral point P is rotated, but it does not alter their orientation. When the sliding contact is 1/3 or 2/3 of the way between two of the apical terminals of the resistor network, the amplified axostat lead should be identical to one of the Einthoven leads or its invert. When the sliding contact is located at one of the apical terminals, the resultant lead should be identical to one of the vector unipolar extremity (vV) leads described by Graettinger and associates.[6] With the contact one-half way between apical terminals the resultant lead is identical to the invert of the one of the vV leads. Thus the axostat may record all of the bipolar and unipolar leads and any desired number of interpolated leads. These relations are depicted graphically in Fig. 2, *B* where all of the lead vectors are represented as arising from the the origin of the figure, and terminating in its elliptical boundary.

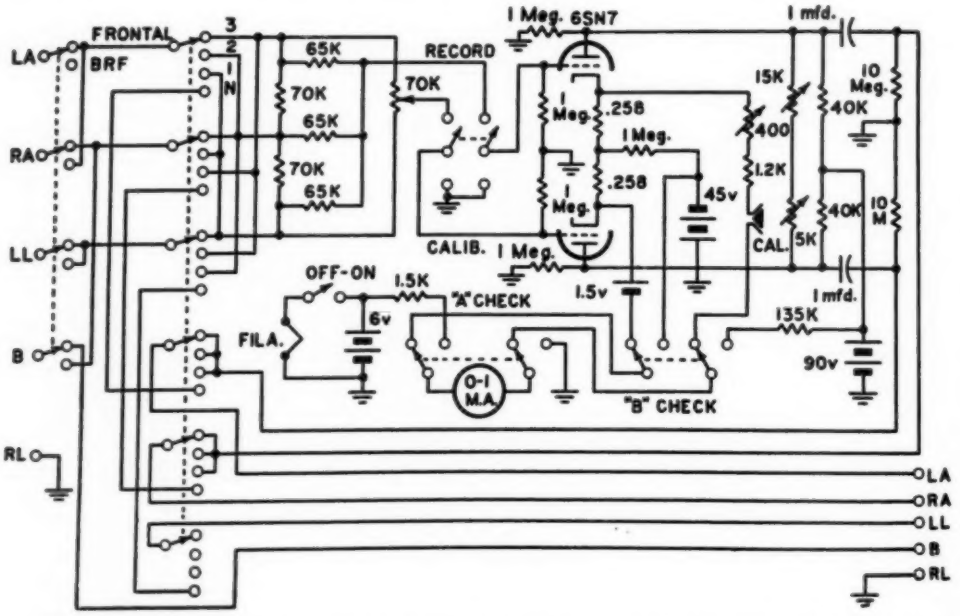

Fig. 3.—Axostat circuitry. The input switching arrangement permits registration from either the frontal plane or *BRF* plane of the Wilson tetrahedron. The "press to test switches" are for checking the strength of the A and B batteries. The lettered terminals in the lower right-hand portion of the illustration indicate the connections to the conventional electronic electrocardiograph which the axostat precedes. Remainder of description in text.

It would be highly desirable to calibrate the axostat in a manner which indicates accurately the direction of its lead vectors. However, for reasons which will be discussed later, it appears impossible to accomplish this objective at the

present time. Therefore, the instrument was calibrated on the basis of an equilateral triangular frame of reference. The effects of this idealization are demonstrated in Fig. 2,*C* where it is seen that the magnitude of all the lead vectors is constant. Accordingly, the axostat synthesizes the extremity potentials of the human body into the manifest potential described by Einthoven and associates,[7] and then records the projection of this potential on any axis passing through the center of the triangular frame of reference.

INSTRUMENTATION

The axostat circuitry is shown in Fig. 3. The delta resistor containing the sliding contact is a wire-wound potentiometer, whereas the other two members of the delta are fixed-wire-wound resistors. A switching arrangement provides a means of connecting these three components together as a delta in any desired combination. When the potentiometer is connected across both arms, the instrument is said to be in range 1; connection of the potentiometer between the right arm and left leg constitutes range 2; and between the left arm and left leg, range 3. These positions are easy to remember since they correspond numerically to the connections of Leads I, II, and III. A pointer on the potentiometer control indicates on an accurately calibrated master dial the angular position of the sliding contact. An outer scale on the master dial indicates the preamplifier gain setting necessary for each position of the sliding contact. Calibration of the master dial is accomplished by adjusting the sliding contact until the resistance between it and the counterclockwise terminal of the potentiometer winding, as measured by a precision Wheatstone bridge, equals the calculated resistance for each particular setting. Employing formulas derived from the preceding theoretical developments, these resistances are calculated in the case by range 3 by

$$\text{Angular position:} \qquad n = \tfrac{1}{2}\left[1 + \frac{1}{\sqrt{3}} \tan\left(\Theta - 30^\circ\right)\right] \qquad (9)$$

$$\text{Preamplifier setting:} \qquad n = \tfrac{1}{2}\left[1 \pm \frac{1}{PS}\sqrt{4 - \frac{(PS)^2}{3}}\right] \qquad (10)$$

where n has the significance described in the preceeding section and is equal to the ratio of the resistance between the sliding contact and the counterclockwise terminal of the potentiometer to the total resistance of the potentiometer winding. PS represents the preamplifier gain setting. This method of calibration obviates any errors which might result from alinearity of the potentiometer winding. The values do not have to be recalculated for the other two ranges since they are reiterative. Data for calibrating the master dial are given in Tables I and II.

The preamplifier gain dial is initially calibrated by actual measurement of the gain for each 5-degree interval. From these data the dial is etched for each 0.05 step in gain, ranging from 1.70 to 3.50. At the beginning of each experiment the gain is arbitrarily set at 3.00 and then the preamplifier adjustment control is rotated until the calibration signal of 0.5 mv. produces a 1.5 cm. deflection on the electrocardiograph.

The relation of the delta resistor values to the Y resistor values is not critical; however, each set should be closely matched (± 0.5 per cent) within itself. The values of each set may be between 65,000 and 100,000 per resistor. The network resistance is therefore of an intermediate magnitude, i.e., it represents a relatively high impedance to the subject and a relatively low impedance to the preamplifier to which it is coupled. This relationship keeps potential losses to approximately 2.5 per cent between subject and network, and 2 per cent between network and preamplifier. For especially accurate work we measure the resistance of each skin electrode, add sufficient series resistance to the two lower-valued electrodes to restore the three-phase balance, and calculate a correction factor from the formula

$$\text{Loss} = \frac{100\ R_S\ (3R_Y + R_\Delta)}{R_S\ (3R_Y + R_\Delta) + R_Y R_\Delta} \quad \text{per cent}$$

where loss = potential drop between subject and network, R_Y = value of each Y resistor, R_Δ = value of each delta resistor and R_S the adjusted resistance of each skin electrode.

TABLE I. DATA FOR CALIBRATING ANGULAR POSITIONS ON THE MASTER DIAL*

RANGE 1 (DEGREES)	RANGE 2 (DEGREES)	RANGE 3 (DEGREES)	n
−150	90	−30	0
−145	95	−25	0.0877
−140	100	−20	0.1559
−135	105	−15	0.2113
−130	110	−10	0.2578
−125	115	−5	0.2979
−120	120	0	0.3333
−115	125	5	0.3654
−110	130	10	0.3949
−105	135	15	0.4226
−100	140	20	0.4491
−95	145	25	0.4747
−90	150	30	0.5000
−85	155	35	0.5253
−80	160	40	0.5509
−75	165	45	0.5774
−70	170	50	0.6051
−65	175	55	0.6346
−60	180	60	0.6667
−55	−175	65	0.7021
−50	−170	70	0.7422
−45	−165	75	0.7887
−40	−160	80	0.8441
−35	−155	85	0.9123
−30	−150	90	1.0000

*Discussion in text.

Both the input and output of the amplifier are double ended (Fig. 3). Since the input leads of the electrocardiograph are connected directly to the grids of the first stage, the axostat is resistance-capacitance coupled to the electrocardio-

graph. The preamplifier tube, a 6SN7GT, is carefully selected for good balance between the two triode sections and low noise level. Noise is further reduced by shock mounting the tube, and employing wire wound controls and metalized plate-load resistors. It was discovered empirically that additional reduction in noise and greater stability of operation could be achieved by interposing a 1-megohm resistor between each plate and ground.

TABLE II. DATA FOR CALIBRATING THE PREAMPLIFIER GAIN SETTING POSITIONS ON THE MASTER DIAL*

PREAMPLIFIER SETTING	n	
1.73	0	1.0000
1.75	0.0069	0.9931
1.80	0.0252	0.9748
1.85	0.0430	0.9570
1.90	0.0599	0.9401
1.95	0.0762	0.9238
2.00	0.0917	0.9083
2.05	0.1067	0.8933
2.10	0.1213	0.8787
2.15	0.1353	0.8647
2.20	0.1489	0.8511
2.25	0.1622	0.8378
2.30	0.1748	0.8252
2.35	0.1873	0.8127
2.40	0.1996	0.8004
2.45	0.2115	0.7885
2.50	0.2231	0.7769
2.55	0.2347	0.7653
2.60	0.2459	0.7541
2.65	0.2570	0.7430
2.70	0.2681	0.7319
2.75	0.2789	0.7211
2.80	0.2897	0.7103
2.85	0.3006	0.6994
2.90	0.3115	0.6885
2.95	0.3224	0.6776
3.00	0.3333	0.6667
3.05	0.3446	0.6554
3.10	0.3562	0.6438
3.15	0.3679	0.6321
3.20	0.3804	0.6196
3.25	0.3936	0.6064
3.30	0.4080	0.5920
3.35	0.4241	0.5759
3.40	0.4439	0.5561
3.45	0.4741	0.5259
3.46	0.5000	

*Discussion in text.

DISCUSSION

Since the axostat leads consist of the algebraic sum of predetermined portions of the Wilson unipolar extremity leads (cf. Equation 3), and the Wilson leads themselves are composed of known proportions of the bipolar extremity leads, it is clear that the axostat leads do not contain any information not inherently present in the bipolar extremity leads. This fact, however, does not preclude

the possibility that axostat leads may be of special value since they represent the projection of the electromotive forces of the heart on a great variety of axes not available in the more conventional type of extremity lead electrocardiography. This is equivalent to "viewing" the cardiac vectors from a great number of points of vantage, and it is possible that certain characteristic abnormal electrocardiographic patterns may be more readily ascertained from a uniquely favorable axostat lead than from the present extremity leads. From a study on electrocardiographic models[3] we concluded that there may be relatively large "uncharted" areas to either side of the Lead I axis. The conclusion was suggested that these areas might profitably be explored with the relatively unrestricted lead vectors available in axostat electrocardiography.

If the human body met the conditions of idealization inherent in the concept of the Einthoven triangle,[7,8] axostat leads would be considered unipolar because the central terminal of the network would be at zero potential. For this reason we sometimes designate axostat leads as vVΘ leads in conformity with the idea of "vector unipolar" extremity leads introduced by Graettinger and associates.[6] The angle of the axis of registration is stated explicitly when desired, leading to a nomenclature of vV23°, vV-136°, etc., as examples of specific axostat leads. Since the potential of the central terminal undoubtedly deviates significantly from zero in most subjects,[9,10] we do not claim that the vVΘ leads are truly unipolar in nature. We feel further that it is of small moment whether they are even approximately unipolar. Any special merit possessed by these leads would appear to lie not in their possible unipolarity, but in the fact that their lead vectors are favorably oriented for the registration of a particular type of electrocardiographic information. This same concept may be applied to the unipolar extremity leads of Wilson and Goldberger since they constitute special cases of the axostat leads. This would provide a sounder understanding of the desirability of certain leads than the older notion of a particular unipolar electrode "looking at" the specific portion of the myocardium which it faces.[11] Furthermore, axostat theory does not make any sharp distinction between the bipolar extremity leads and the so-called unipolar extremity leads, but demonstrates that they are all special cases of a general type of extremity lead. This concept is in accord with that formulated by Graettinger and associates,[6] and we agree with their conclusion that the bipolar extremity electrocardiograms had best not be abandoned.

At the present time, the angular calibration of the instrument is based on an equilateral triangular frame of reference despite the fact that it might be more desirable to base the calibration on the scalene triangle of Burger. The chief reasons for this arbitrary choice of a frame of reference are that the configuration of the Burger triangle is probably not accurately known for the human body, and it undoubtedly varies from subject to subject. Furthermore, there is some evidence that the configuration of the Burger triangle is variable within the cardiac region of a given subject,[3] and at the present time our analysis of fundamental theory leads us to believe that there is no method for accurately establishing a "mean" Burger triangle for the subject. On the other hand, the Ein-

thoven triangle has been a well established device in electrocardiographic analysis for many years and much valuable information has resulted from its application. However, the possibility should not be discounted that eventually sufficient knowledge of the Burger triangle will be gained to warrant its superseding the Einthoven triangle.

SUMMARY

1. A new instrument is described which produces any desired number of interpolated leads between the extremity leads of the electrocardiogram.

2. An analysis of the new leads in terms of lead vectors demonstrates that they represent the projection of the electromotive forces of the heart on any axis of the Burger triangle.

3. Some of the problems in which this instrument may possess unique investigative value are discussed.

4. Bipolar and unipolar extremity leads are shown to constitute special cases of a general type of extremity lead. On the basis of a priori reasoning it cannot be concluded that the bipolar leads are inferior to unipolar leads and should, therefore, be abandoned in their favor.

APPENDIX

The following trigonometric derivation of axostat theory is limited to the idealized case of the equilateral triangle, but it may be of greater significance to the reader who is not familiar with vector algebra than the development in terms of lead vectors. By referring to Fig. 1,

$$E_C = 1/3\,(E_R + E_L + E_F) \tag{1}$$

where E_C is the potential at the center of the network, and E_R, E_L, E_F are, respectively, the potentials at the right arm, the left arm, and the left leg. By assuming the peripheral members of the network to be linear resistors, the potential at the sliding contact, P, will be

$$E_P = nE_F + (1 - n)\,E_L \tag{2}$$

where E_P is the potential at the point P, and n has the significance of proportionality previously described. After substituting the identity,

$$n = \frac{\cos\theta + \sqrt{3}\sin\theta}{\sqrt{3}\,.\,2\cos(\theta - 30°)}$$

In Eq. (2) and subtracting Eq. (1) from it,

$$E_P - E_C = \frac{(E_L - E_R)\cos\theta + (1/\sqrt{3})(2E_F - E_R - E_L)\sin\theta}{\sqrt{3}\,.\,2\cos(\theta - 30°)} \quad . \tag{3}$$

Making the substitutions $E_1 = E_L - E_R$, $E_2 = E_F - E_R$, and $E_3 = E_F - E_L$, where E_1, E_2, and E_3 are Leads I, II, and III, respectively; this gives

$$E_P - E_C = \frac{E_1\cos\theta + \dfrac{E_2 + E_3}{\sqrt{3}}\sin\theta}{\sqrt{3}\,.\,2\cos(\theta - 30°)} \quad . \tag{4}$$

If by means of the preamplifier we arbitrarily increase the potential difference between the sliding contact and the center of the network by a factor of $\sqrt{3} \cdot 2 \cos (\theta - 30°)$ the output of the axostat, E_X, will be

$$E_X = E_1 \cos \theta + \frac{E_2 + E_3}{\sqrt{3}} \sin \theta \quad . \tag{5}$$

This last equation can be reduced to the form

$$E_X = E_m \cos (\theta - \alpha) \tag{6}$$

where

$$\left.\begin{aligned} E_m &= \sqrt{E_1^2 + \frac{(E_2 + E_3)^2}{\sqrt{3}}} \\ \alpha &= \tan^{-1}[(E_2 + E_3)/\sqrt{3}\, E_1] \end{aligned}\right\} \tag{7}$$

It is apparent from Eq. (5) and Eq. (6) that the axostat synthesizes the instantaneous potentials of the conventional bipolar extremity leads into a series of vectors having the magnitudes and directions indicated by Eq. (7). Since the vertical component of E_m is $(E_2 + E_3) / \sqrt{3}$ and the horizontal component is E_1, the manifest potential of Einthoven[12] and E_m are identical. According to Eq. (6), the tracings produced by the "axostat" represent a plot, with respect to time, of any desired component of the manifest potential.

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THE C-REACTIVE PROTEIN DETERMINATION AS A MEASURE OF RHEUMATIC ACTIVITY

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IN sera of patients acutely ill with pneumococcal pneumonia Tillett and Francis[1] described the presence of a substance which formed a precipitate with a dilute solution of the somatic polysaccharide isolated from the body of the pneumococcus. This reaction was also observed in the sera of patients actuely ill with rheumatic fever, subacute bacterial endocarditis, and lung abscess. Ash[2] reported the presence of this abnormal reaction in sera of children during the acute phase of infections caused by the colon-typhoid group of bacilli. This substance was not found in the sera of patients with chorea, tuberculosis, congenital syphilis, measles, or in patients with rheumatic heart disease without active rheumatic infection. Löfström[3] demonstrated the presence of this substance in a variety of infectious and noninfectious diseases. In the latter group, there were patients with myocardial infarction and fever and patients who had received injections of sulfur-containing material.

Abernethy and Avery[4] reported this reactive substance to be a protein associated with the albumin fraction of human serum. Electrophoretic studies by Perlman and associates[5] demonstrated that the C-reactive protein migrated with the alpha globulin, probably the alpha-1 fraction. After isolating the C-reactive protein in pure form, McLeod and Avery[6] were able to show that it differed chemically and immunologically from the proteins found in the sera of healthy persons. They produced a specific rabbit antiserum to the isolated C-reactive protein, which did not react with normal human-serum proteins.

In recent years, several groups of investigators[7-10] have reported the value of the C-reactive protein determination in acute rheumatic fever. It is generally agreed that the test is of no specific diagnostic value and cannot be used in differentiating rheumatic fever from other febrile illnesses which present similar clinical pictures. However, it seems to be a sensitive index of the presence of rheumatic activity. With rare exception it has been found in the sera of patients in the acute stage of rheumatic fever. This protein disappears from the blood

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Aided by a grant from the Mildred Forman Foundation.

Received for publication May 10, 1954.

TABLE I

NO.	NAME	AGE	SEX	COLOR	DIAGNOSIS	ATTACK	TREATMENT	BEFORE TREATMENT		EFFECT OF TREATMENT	REMARKS
								C-PROTEIN	SED. RATE MM./HR.		
1.	T. McG.	13	F.	W.	Acute carditis	Second	Cortisone	2 plus Neg.	48 20	Negative on 29th day of cortisone (sed. rate 22 mm./hr.); 2 plus 41 days after treatment (sed. rate 48 mm./hr.); 1 plus 137 days after treatment (sed. rate 33 mm./hr.)	Persistent positive test after treatment was indicative of continued low-grade activity; C-reactive protein temporarily suppressed by cortisone
2.	B.C.	11	F.	N.	Acute carditis	Third	Cortisone	3 plus	38	Negative on 47th day of cortisone (sed. rate 1 mm./hr.); 1 plus 8 days after treatment (sed. rate 28 mm./hr.); Negative 53 days after treatment (sed. rate 32 mm./hr.)	Persistent low-grade activity
3.	B.F.	9	M.	W.	Chorea and acute carditis	Second	Cortisone	Not done	—	Test done once 50 days after treatment and was found 2 plus (sed. rate 17 mm./hr.)	Positive C-reactive protein in patient with chorea plus carditis; persistent activity
4.	E.W.	13	F.	W.	Chorea and acute carditis	Second	Salicylates	2 plus	25	Test not repeated	Positive C-reactive protein in chorea plus carditis
5.	H.McC.	9	M.	W.	Acute rheumatic fever; carditis?	Second	Cortisone	Not done	—	No test done during cortisone because of lack of material; 1 plus 8 days after treatment (sed. rate 45 mm./hr.); 2 plus 36 days after treatment (sed. rate 35 mm./hr.); 1 plus 63 days after treatment (sed. rate 28 mm./hr.); Negative 3½ months after treatment (sed. rate 15 mm./hr.)	Persistent low-grade activity
6.	C.H.	5	F.	N.	Acute carditis	Second	Cortisone	Neg.	38	2 plus 13 days after cortisone (sed. rate 37 mm./hr.); Negative 2 months after treatment (sed. rate 9 mm./hr.)	Negative C-reactive protein in presence of active carditis; persistent activity
7.	A.R.	13	M.	W.	Acute carditis	Seventh	Cortisone	2 plus	40	Trace on 13th day of cortisone (sed. rate 17 mm./hr.); Test not repeated	

W. = white; N. = Negro.

W. = white; N. = Negro.

8.	A.B.	11½	F.	W.	Acute carditis	First	Cortisone	Not done	—	Negative on 16th day of cortisone (sed. rate 38 mm./hr.); 4 plus 7 days after treatment (sed. rate 45 mm./hr.); Negative 3 months after treatment (sed. rate 22 mm./hr.)	Laboratory rebound
9.	G.C.	9½	F.	W.	Acute carditis	Second	Cortisone	2 plus	40	Test not done during cortisone; 2 plus 8 days after treatment (sed. rate 48 mm./hr.); Negative 30 days after treatment (sed. rate 40 mm./hr.)	Laboratory rebound; negative C-reactive protein better guide than sed. rate
10.	G.R.	9	M.	W.	Acute carditis	Second	Cortisone	3 plus	40	Test not done during cortisone; negative 14 days after treatment (sed. rate 18 mm./hr.)	
11.	S.G.	7½	F.	W.	Acute carditis	Second	Cortisone	3 plus	43	Negative 23rd day of cortisone (sed. rate 5 mm./hr.); Negative 10 days after treatment (sed. rate 36 mm./hr.)	Negative C-reactive protein better guide than sed. rate
12.	P.G.	6	F.	W.	Acute carditis	First	Cortisone	Not done	—	1 plus 5 days after cortisone (sed. rate 27 mm./hr.)	Laboratory rebound
13.	L.R.	10	M.	W.	Acute carditis	First	ACTH	Not done	—	Not done during ACTH; 3 plus 38 days after treatment (sed. rate 20 mm./hr.); Trace 53 days after treatment (sed. rate 1 mm./hr.)	Low-grade activity; positive C-reactive protein in presence of normal sed. rate
14.	P.T.	9	F.	W.	Acute rheumatic fever; no carditis	First	Cortisone	Not done	—	Test not done during cortisone; 1 plus 10 days after treatment (sed. rate 40 mm./hr.); Negative 3 months after treatment (sed. rate 27 mm./hr.)	Persistent activity; negative C-reactive protein better guide than sed. rate
15.	H.B.	12	M.	W.	Acute rheumatic fever; ? carditis	Fourth	Symptomatic	1 plus	42	Test not repeated	C-reactive protein helped to determine presence of activity
16.	M.M.	11	F.	W.	Acute carditis	First	Cortisone	Not done	—	1 plus on 35th day of cortisone (sed. rate 7 mm./hr.)	Only one test done because of lack of reagent
17.	J.O.	3½	M.	W.	Acute rheumatic fever; ? carditis	First	Cortisone	Not done	—	Negative 17 days after cortisone (sed. rate 40 mm./hr.)	Only one test done; negative C-reactive protein better guide than sed. rate

TABLE I (CONTINUED)

NO.	NAME	AGE	SEX	COLOR	DIAGNOSIS	ATTACK	TREATMENT	BEFORE TREATMENT		EFFECT OF TREATMENT	REMARKS
								C-PROTEIN	SED. RATE MM./HR.		
18.	S.S.	15	M.	W.	Acute rheumatic fever; carditis ?	Second	Cortisone	Not done	—	Negative 13th day cortisone (sed. rate 35 mm./hr.); 3 plus on day treatment stopped (sed. rate 46 mm./hr.); 1 plus 7 days after treatment (sed. rate 43 mm./hr.); Negative 21 days after treatment (sed. rate 38 mm./hr.)	Laboratory rebound; negative C-reactive protein better guide than sed. rate
19.	E.G.	11	F.	W.	Acute carditis	First	Hydrocortisone	Not done	—	Negative 8th day hydrocortisone (sed. rate 6 mm./hr.); Negative 2 days after treatment (sed. rate 50 mm./hr.)	
20.	J.C.	15	M.	W.	Acute carditis; congestive heart failure	Second	Cortisone	Not done	—	Test not done during cortisone; negative 40 days after treatment (sed. rate 39 mm./hr.) Negative 69 days after treatment (sed. rate 14 mm./hr.)	Negative C-reactive protein better guide than sed. rate
21.	E.K.	13	M.	W.	Acute carditis	First	Cortisone	Not done	—	Test not done during cortisone; Negative 2 weeks after treatment (sed. rate 20 mm./hr.); Negative 6 weeks after treatment (sed. rate 17 mm./hr.)	Negative C-reactive protein better guide than sed. rate
22	L.O.	17	M.	W.	Acute carditis and pericarditis	Second	Cortisone	Not done	—	Test not done during cortisone; 1 plus 6 weeks after treatment (sed. rate 45 mm./hr.); Negative 10 weeks after treatment (sed. rate 50 mm./hr.)	Positive C-reactive protein along with elevated sed. rate indicative of continued activity
23.	P.B.	20	F.	W.	Chronic rheumatic fever, active	Sixth	Symptomatic	1 plus	52	Test not repeated	Positive C-reactive protein is in agreement with the elevated sed. rate and clinical picture
24.	C.G.	18	F.	W.	Acute rheumatic fever, inactive	First	Salicylates	Not done	—	Negative 1 month after salicylates (sed. rate 36 mm./hr.)	Negative C-reactive protein better guide than sed. rate

with subsidence of activity, in most instances, before there is a fall in the erythrocyte sedimentation rate. It reappears, along with the results of other abnormal laboratory tests, after withdrawal of ACTH or cortisone therapy.[8]

MATERIALS AND METHODS

This report deals with observations made on twenty-four patients hospitalized in the rheumatic fever wards of the Jewish Sanitarium and Hospital for Chronic Diseases. These patients were children, adolescents, and adults admitted early in the acute phase of their rheumatic infection, as well as those transferred from other institutions during convalescence or chronic activity (Table I). All but one (No. 24) had active rheumatic fever. Eleven were males and thirteen were females. Two patients (No. 3, 4) had chorea and carditis. Eighteen patients were treated with cortisone*; one received ACTH and one hydrocortisone*; the other four received salicylate therapy.

The patients were followed by the same group of pediatricians and cardiologists. X-ray, fluoroscopy of the heart, and electrocardiograms were done frequently at the onset of the disease and on an average of once a month during convalescence. The white blood cell count, erythrocyte sedimentation rate,[11] and plasma fibrinogen[12] were done at least once a week. The cephalin-cholesterol flocculation,[13] zinc turbidity,[14] thymol turbidity,[15] and gamma globulin precipitation tests[16] were also done once a week. In this study, the absence of activity was judged by the complete and persistent subsidence of all clinical and laboratory manifestations of the disease.

Because of the limited amount of C-reactive protein antiserum† available to us, the test was not performed at frequent intervals. Instead, tests were done at strategic points in the clinical course. The C-reactive protein determinations were performed according to the method of Anderson and McCarty.[7] Briefly, 1.5 cm. each of the patient's serum and C-reactive protein antiserum were drawn into a capillary tube (external diameter about 1 mm.) and incubated for two hours at 37°C. The degree of precipitation (0 to 4-plus) was read after overnight refrigeration. One-millimeter precipitation was considered 1-plus.

RESULTS

Of ten patients with active disease whose sera were tested for C-reactive protein before hormone therapy all but one (No. 6) had amounts varying from 1-plus to 3-plus. Another patient (No. 1) had a 2-plus precipitation shortly after admission, but when the test was repeated 14 days later it was negative despite rheumatic activity.

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*We are indebted to Dr. Elmer Alpert and Dr. Augustus Gibson of Merck & Co. Inc., Rahway, N. J., for their generous supplies of cortisone and hydrocortisone used in this study.

†We are indebted to Dr. Harrison F. Wood, of the Rockefeller Institute for Medical Research, for supplying us with the rabbit antiserum and for his help toward the preparation of the antiserum in our laboratory.

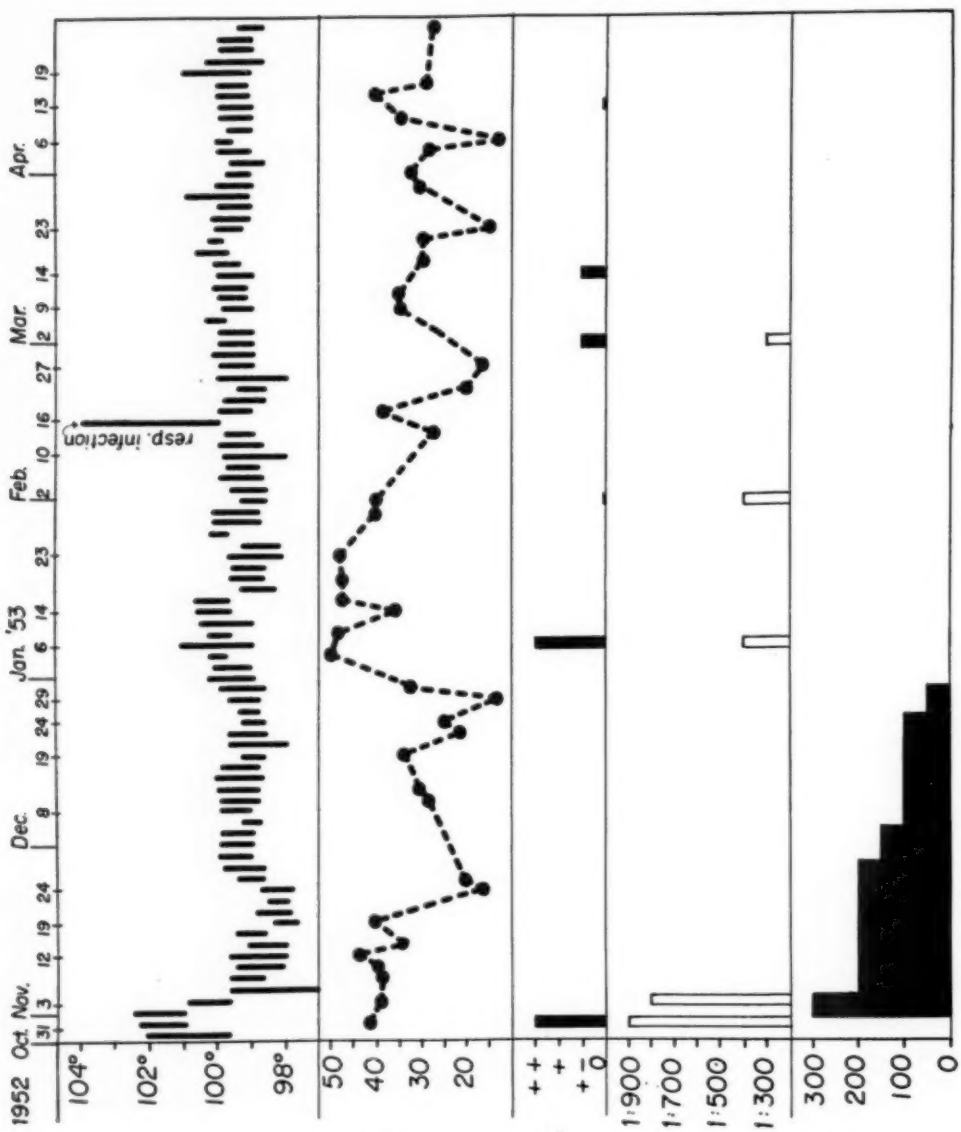

Fig. 1.—Patient G. C. 9½-year-old girl.

The sera of eight patients were tested during hormone treatment. Six of these had a negative C-reactive protein. We cannot state with any certainty when, during the course of treatment, the test first became negative, since the test was not repeated at frequent intervals. In our series, the earliest disappearance of this abnormal protein from the serum was on the eighth day of treatment (No. 19). It is clear that cortisone and hydrocortisone caused the disappearance of the C-reactive protein from the sera of these six patients. However, a trace (No. 7) and 1-plus (No. 16) reaction were still present in two patients on the thirteenth and thirty-fifth days, respectively.

Of the eighteen patients whose sera were tested after hormone therapy, twelve showed a positive test at some time after therapy had been discontinued. In one patient (No. 18) the C-reactive protein was 3-plus on the day cortisone was discontinued, after the dose had been tapered. As can be seen from Table I, a positive test either represented a rebound phenomenon (No. 8, 9, 12, 18) or continued rheumatic activity (No. 1-6, 13, 14, 22). One patient (No. 13) with continued low-grade activity and a trace of C-reactive protein had a normal sedimentation rate. Eight of these twelve patients subsequently had a negative C-reactive protein test. Of these, six had a rapid sedimentation rate. The C-reactive protein was a better guide to activity than the sedimentation rate.

The six patients with negative C-reactive protein reactions after hormone therapy were inactive clinically. All showed a slight-to-moderate elevation of the erythrocyte sedimentation rate which continued elevated for a period of one-to-eight weeks. This is to be expected because the C-reactive protein determination was done because of disparity between the rapid sedimentation rate and the clinical picture. After careful follow-up it was established that here again the C-reactive protein determination was a more accurate measure of the inactive state.

Fig. 1.—Patient G. C. 9½-year-old girl.

ILLUSTRATIVE CASE REPORTS

CASE 1.—A patient with protracted elevation of the sedimentation rate and negative C-reactive protein (Fig. 1). G. C. (No. 9), a 9½-year-old white girl was admitted on Oct. 29, 1952, with the chief complaint of fatigue and pain in her left foot. Since the age of 6 years, she had repeated episodes of epistaxis. About 2 years before admission, she complained of fever and pain in both heels. She responded to penicillin and was allowed out of bed in a week.

The present illness was ushered in by an attack of tonsillitis one month before the onset of acute polyarthritis. When the patient was admitted on the eighteenth day of her illness, she had involvement of numerous small and large joints in addition to periarticular erythema of both elbows. Her temperature on admission was 99.6° F. but rose to 102° F. the next day. Two days after admission the C-reactive protein in her serum was 2 plus. The blood sedimentation rate and gamma globulin were elevated. The antistreptolysin "O" titer was 1:900 (normal 1:50). Cortisone was started on the fifth day of hospitalization and continued for 58 days for a total dose of 7.25 Gm. The fever subsided within 48 hours and the sedimentation rate fell to normal in 22 days. Forty-eight hours after cessation of therapy, there was a rise in temperature to 100.8° F. and elevation of the sedimentation rate to 43 mm./hour. The C-reactive protein was 2 plus, 8 days after cortisone. At this time, the sedimentation rate was 48 mm./hr., and the temperature was 101.2° F. On the thirty-third day after treatment the C-reactive protein was negative when the sedimentation rate was still 40 mm./hr. Fourteen days later she suffered from a respiratory infection with a temperature of 104° F. which was followed by a trace of C-reactive protein in the

serum. Fifteen weeks after treatment the test was again negative, but the sedimentation rate was 38 mm./hr. At this time there was no clinical evidence of rheumatic activity. The patient was ambulated and discharged 14 days later although the sedimentation rate remained somewhat elevated. When she was next seen in the Outpatient Department six weeks later, she was clinically well and her blood sedimentation rate was still elevated to 30 mm./hr.

In this case, the negative C-reactive protein was a better index of activity than the erythrocyte sedimentation rate which remained elevated for 8 weeks after the C-reactive protein had become negative.

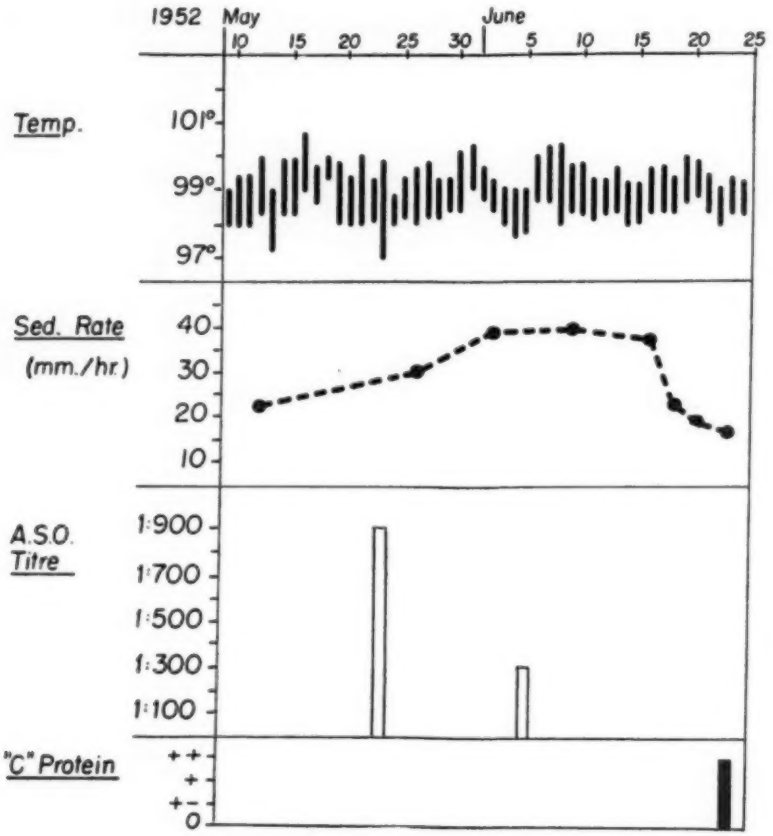

Fig. 2.—Patient B. F. 9-year-old boy.

CASE 2.—A positive C-reactive protein in a patient with chorea and carditis (Fig. 2). B. F. (No. 3), a 9-year-old white boy, was admitted to another hospital on April 21, 1952, with a 5-day history of choreiform movements. He was treated with penicillin, phenobarbital, and cortisone. He received a total of 1.1 Gm. of cortisone in 8 days. A systolic murmur was heard at the apex. The P-R interval was 0.18 sec. and prolonged for the ventricular rate. The patient improved clinically and was transferred to the Jewish Sanitarium and Hospital for Chronic Diseases on May 29, 1952. A harsh, blowing systolic murmur was heard at the apex and was transmitted to the left sternal border and to the left axilla. His course was characterized by a low-grade fever between 100° and 100.6° F. The sedimentation rate fluctuated between 23 and 40 mm./hr. during the first month and gradually fell to 17 mm./hr. one day before transfer to a hospital in Miami, Florida. On this day, the C-reactive protein was 2 plus. Follow-up data from the hospital in Miami indicated a course of protracted low-grade activity.

The demonstration of C-reactive protein in this child with chorea and in patient E. W. (No. 4) with chorea was probably due to the associated smoldering carditis.

CASE 3.—A patient with active carditis, rapid sedimentation rate, and a negative C-reactive protein (Fig. 3). C. H. (No. 6), a 5-year-old Negro girl, gave a history of frequent sore throats and several hospital admissions for congestive heart failure. Upon admission to the Jewish Sanitarium and Hospital for Chronic Diseases on July 28, 1952, physical examination revealed an undernourished chronically ill child. The left chest was prominent. A harsh, loud systolic murmur was audible over the entire precordium, left axilla, and back. The second pulmonic sound was accentuated. Fluoroscopic and x-ray examination revealed a heart consistent with the diagnosis of advanced mitral valve disease. There was no evidence of congestive failure.

The course was characterized by a recurrent apical diastolic murmur, overactive heart sounds, a change in the quality of the apical systolic murmur, a low-grade temperature, and rapid sedimentation rate. A C-reactive protein determination on Sept. 8, 1953, was negative.

Despite this finding, cortisone therapy was instituted four days later, because during this time, there was tachycardia during sleep, and "overactive" heart, and a high-pitched musical murmur of the "sea-gull" type. She received a total of 8.6 Gm. during 53 days. Within eight days of therapy, the sedimentation rate became normal and the clinical signs of carditis abated. Her course during cortisone was complicated by congestive heart failure due to salt and water retention which responded to digitalis and Mercuhydrin and which did not necessitate withdrawal of cortisone. Twelve days after treatment the serum showed a 2-plus C-reactive protein. The temperature and sedimentation rate were elevated, and the heart was again overactive. Low-grade activity continued for 2 months.

On Jan. 8, 1953, she was afebrile, the C-reactive protein was negative, and the sedimentation rate was normal.

This patient and patient T. M. G. (No 1; Fig. 4) are the only two in our series where the C-reactive protein was negative in the presence of rheumatic activity. It is interesting to note that C-reactive protein was present in the period of low-grade activity which followed cortisone therapy.

COMMENT

It is generally accepted that there is no single laboratory procedure which is specific for the diagnosis of rheumatic fever or for the determination of activity once the diagnosis has been established. The determination of the C-reactive protein has been proposed as the most useful indicator of rheumatic activity.[7-10] In our series of patients, a negative C-reactive protein determination was by far superior to the sedimentation rate which usually remained abnormal for one to eight weeks after the C-reactive protein had become negative.

A negative C-reactive protein test was used by the authors as a guide in ambulating clinically inactive patients in the presence of a persistently elevated erythrocyte sedimentation rate. Whenever possible, the test was repeated a week or two after the patient had been out of bed. If the test remained negative, the patient was discharged from the hospital. Follow-up of these patients has not shown any progression of the disease.

We have encountered two patients with negative C-reactive protein in the presence of rheumatic activity. From Fig. 4 it can be seen that the C-reactive protein which was initially 2 plus at the time the sedimentation rate was 45 mm./hr. was negative 14 days later. At this time, however, rheumatic activity was characterized by a protodiastolic gallop, a tachycardia, and a variable apical diastolic murmur. In addition, the electrocardiogram showed an increased P-R interval and T-wave inversion in the precordial leads. She was treated with cortisone. The other patient in our series, C. H. (Fig. 3), has already been discussed.

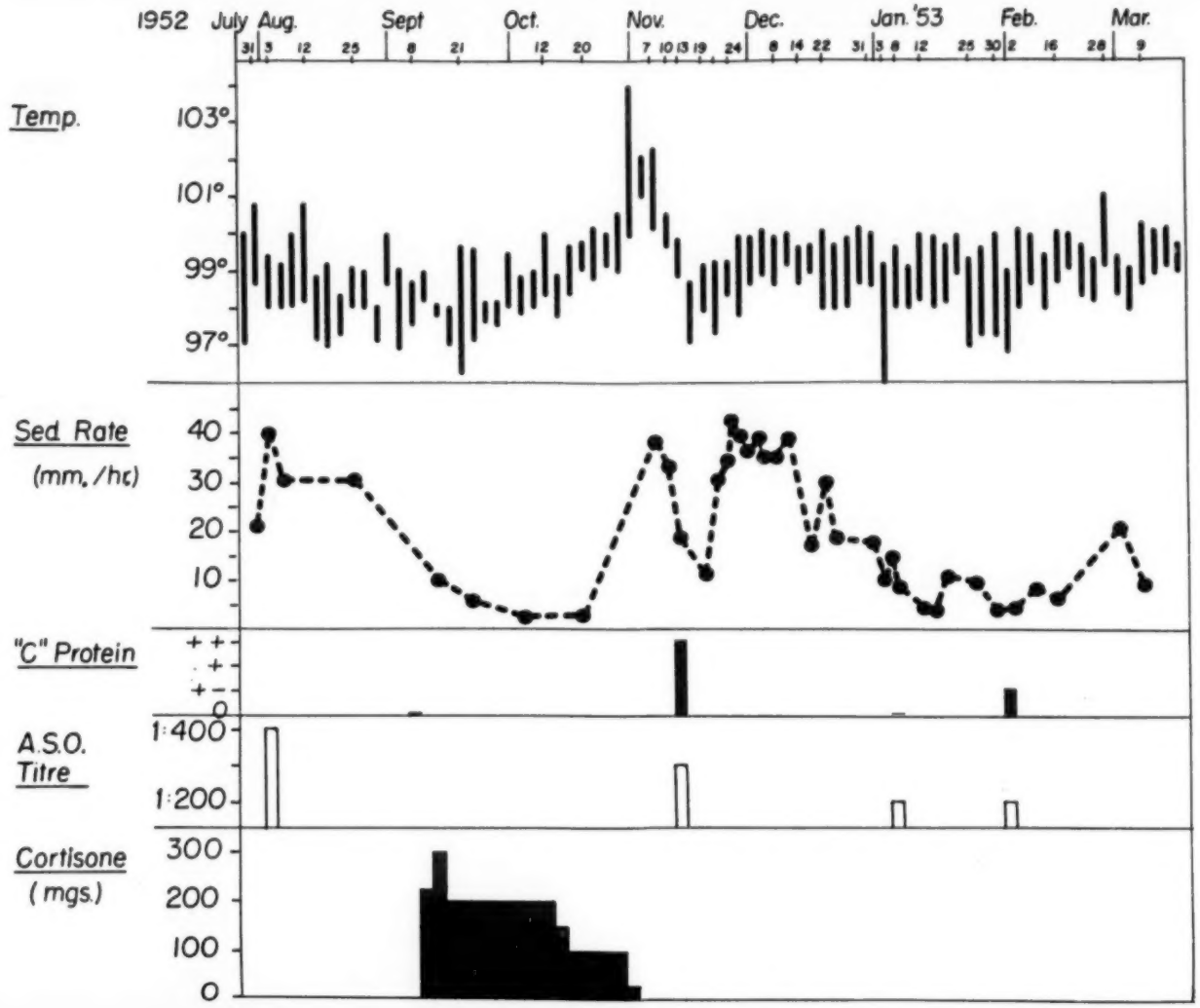

Fig. 3.—Patient C. H. 5-year-old girl.

Fig. 3.—Patient C. H. 5-year-old girl.

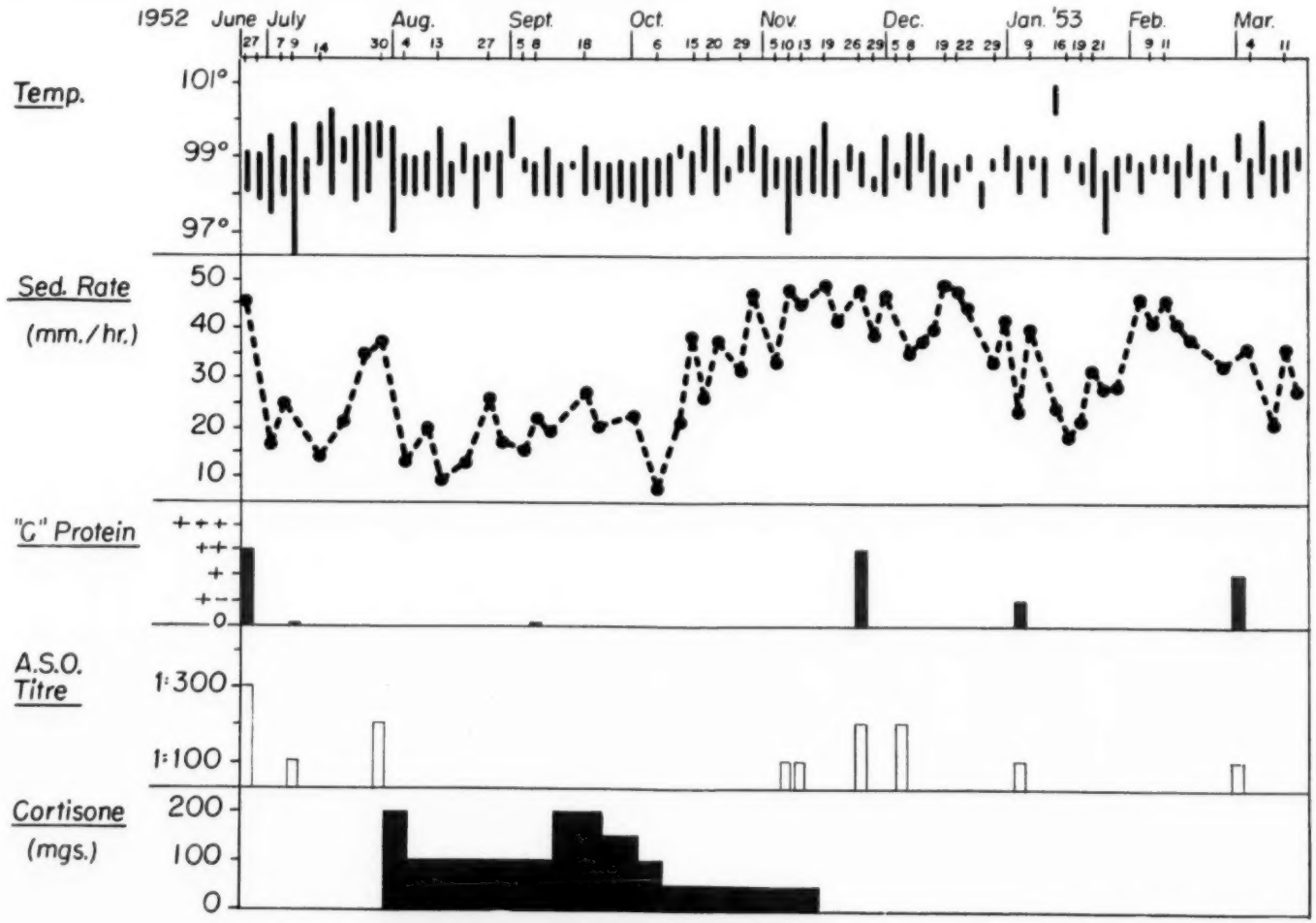

Fig. 4.—Patient T. Mc. G. 13-year-old girl.

Stollerman and associates[10] and Hill[17] have reported similar findings, which indicate that in rare instances, the C-reactive protein may not mirror activity of the rheumatic process. Stollerman's patient had chorea, slight elevation of the sedimentation rate, and soft apical and basal systolic murmurs of "possible" significance. He was classified as having rheumatic activity on the basis of the criteria of activity used by the authors. In the case of Hill's patient, however, it is only fair to point out that the less sensitive C-polysaccharide-precipitation test[18] was used.

The blood sedimentation rate, fibrinogen, gamma globulin, and the C-reactive protein tests return to normal with cortisone therapy and reappear as part of the laboratory-rebound phenomenon. None of these tests can, therefore, be used in the differential diagnosis of rebound from continued rheumatic activity. Only clinical observation for a period of at least 3 weeks, without reinstitution of therapy, can differentiate between the two. Eight of the twelve patients in our series who had a reappearance of a positive C-reactive protein after therapy proved on clinical observation to have continued rheumatic activity which subsequently subsided spontaneously.

Reports in the literature[2,7,10] have indicated that patients with Sydenham's chorea fail to show C-reactive protein in their sera at any stage of the disease. The presence of the C-reactive protein in the sera of the two patients with chorea in our series suggests that a positive test in chorea may be indicative of an associated carditis.

SUMMARY

1. C-reactive protein determinations were performed on the sera of twenty-four rheumatic fever patients in order to help determine the presence or absence of activity.

2. There was a close correlation between the inactive state and a negative C-reactive protein determination. However, there were two instances of a negative C-reactive protein in the presence of rheumatic activity.

3. A positive test in Sydenham's chorea should suggest the presence of an associated carditis.

4. The C-reactive protein determination was a better guide to activity than the sedimentation rate which showed protracted elevation despite the inactive state.

We wish to thank Dr. Solomon R. Slater for his advice and assistance.

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AN EVALUATION OF ELECTROPHORESIS IN RHEUMATIC FEVER

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FRACTIONATION of the plasma proteins in rheumatic fever by conventional salting-out techniques has not shown any consistent diagnostic pattern. A decrease in the serum albumin and rise in the serum globulin with a reversal of the albumin/globulin ratio may occur. Plasma fibrinogen may be elevated, particularly during acute phases of the disease. The protein flocculation reactions have not provided a uniform, reliable indication of the active rheumatic state. Previously reported electrophoretic studies[1-6] have also failed to establish a characteristic diagnostic pattern and have not differentiated the immune response of the rheumatic from the nonrheumatic patient, particularly following streptococcal disease.

With these limitations in mind, electrophoresis was employed together with the sedimentation rate, blood fibrinogen, protein flocculation tests, and the C-reactive protein determination, in order to help determine the presence or absence of rheumatic activity. An analysis of these electrophoretic patterns is the basis for this presentation.

MATERIAL AND METHODS

From 1951 to 1953, 77 electrophoretic determinations were done on the sera of thirty-seven patients with rheumatic fever. This report concerns itself with 40 of these determinations. Many of the determinations were done when the diagnosis of rheumatic activity was of prime importance but difficult to assess clinically. None of the patients tested received ACTH or cortisone. Blood was obtained in the fasting state.

The electrophoretic determinations were done by the Department of Laboratories* on clear, unhemolyzed serum. The analyses were carried out in the portable Aminco-Stern electrophoresis apparatus. This instrument employs the moving-boundary technique of Tiselius, and records are made by a highly

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Aided by a grant from the Mildred Forman Foundation.

Received for publication May 10, 1954.

*We wish to thank Mr. A. Saifer, Biochemist, and Mr. H. Oreskes for their assistance.

sensitive schlieren optical system according to Philpot[7] and Svensson.[8] The serum was diluted (1:2 or 1:3) with barbiturate buffer (pH 8.6 to 8.7, ionic strength 0.1) and then dialyzed against an excess of buffer for 48 hours in a refrigerator, or in a mechanical dialyzer for at least 2 hours at 4° C. Electrophoresis was carried out for about one hour at 14 to 15 milliamperes and 2° C. The patterns were then photographed. All calculations were done from the ascending pattern which gave better diagrams and no beta anomaly. The photographs were enlarged three and one-half times, traced on paper, and the areas measured with a planimeter according to the method of Longsworth.[5]

A review of the literature was made in order to establish a set of normal values for the various electrophoretic protein fractions. These data are incorporated in Table I. The large series of Reiner and associates[15] on sera of normal males and females was considered the best guide in determining deviations from the normal. As can be seen, theirs was the largest series on electrophoresis of serum proteins. Many of the other studies were on plasma samples.[10-12]

In our series, a protein fraction was considered abnormal if its value varied from the normal mean of Reiner and associates by two standard deviations or more. These abnormal values are tabulated in italics. A change was considered slight if the value varied by less than two standard deviations. These slight changes have not been considered abnormal but have been listed under "Comment" in the tabulation of our results (Table II).

The serum total protein was determined with the biuret reagent of Gornall and associates.[16] The blood sedimentation rate was determined by the method of Wintrobe.[17] The C-reactive protein was determined* as described by Anderson and McCarty.[18]

RESULTS

The electrophoretic patterns have been grouped according to the type and number of abnormalities present (Table II). It is immediately apparent that there are various possible combinations of abnormal protein fractions in rheumatic fever. Furthermore, the duration of rheumatic activity is not the only factor which increases the number of abnormalities. The severity of the illness is the more important factor.

The alpha-1 globulin fraction, as an isolated abnormality, was not encountered in this series. The beta globulin fraction was more frequently elevated than previously reported in the literature and was elevated as early as 21 days. It was an isolated abnormality in two instances. The alpha-2 globulin fraction was very frequently elevated either by itself or in combination with the other globulins. It was elevated as early as 4 days and as late as 1½ years. An elevated alpha-2 fraction was frequently associated with nonrheumatic inflammation. An elevated gamma globulin fraction was observed in the presence of rheumatic activity whether or not the rheumatic fever was preceded by a respiratory infection. In a few instances of rheumatic activity, the gamma globulin was normal despite a preceding respiratory infection.

*We wish to thank Dr. Harrison F. Wood, Rockefeller Institute for Medical Research, for furnishing the C-protein antiserum.

TABLE I

AUTHORS	MATERIAL		TOTAL PROTEIN (GRAM %)	% TOTAL PROTEIN (AREA)						PROTEIN (GRAM %)						
				ALBUMIN	GLOBULIN					ALBUMIN	GLOBULIN					A/G RATIO
					ALPHA-1	ALPHA-2	BETA	FIBRINOGEN	GAMMA		ALPHA-1	ALPHA-2	BETA	FIBRINOGEN	GAMMA	
Dole and Braun[10]	15 plasmas	Mean	—	60.3	4.6	7.2	12.1	5.1	11.0	4.04	0.31	0.48	0.81	0.340	0.74	1.53
		S.D.	—	2.8	.7	1.3	1.9	0.6	2.5	0.27	0.051	0.083	0.126	0.059	0.151	0.181
Armstrong et al.[11]	20 plasmas pool	Mean	—	55.2	5.3	8.7	13.4	6.5	11.0	—	—	—	—	—	—	—
		S.D.	—	1.3	.5	—	1.6	.6	.7							
Lubschez[12]	26 plasmas 4 sera	Mean	—	58.8	4.9	9.5	12.6	5.3	9.5	—	—	—	—	—	—	—
		S.D.	—	6.9	1.5	2.0	2.9	1.8	3.6							
Cooper et al.[13]	13 sera	Mean	—	59.9	3.4	8.8	12.8	—	15.1	—	—	—	—	—	—	—
		S.D.	—	2.9	1.1	1.4	1.8	—	2.5							
Beiler et al.[14]	7 sera	Mean	6.8	59.5	13.8		13.4	—	13.4	—	—	—	—	—	—	1.50
		Range	6.1-7.5	53-69.9	9-19		11-18	—	10-17							1.1-2.2
Reiner et al.[15]	80 sera	Mean	7.23	56.0	7.2	8.8	13.1	—	14.7	4.3	0.50	0.6	0.9		1.0	1.29
		S.D.	.54	2.8	1.3	1.9	2.5	—	2.6	0.33	0.11	0.17	0.27		0.21	0.16

S.D. = Standard deviation

Decrease of the albumin fraction with reversal of the A/G ratio was a most frequent finding.

The group with normal electrophoretic patterns included patients with the postinfectious state, inactive rheumatic fever, and active rheumatic fever with carditis and chorea. At times, the normal electrophoretic pattern corroborated the inactive state when the sedimentation rate was normal, or even slightly elevated. However, a normal pattern was misleading in mild rheumatic activity of 5 months and 2 years duration, and was not prognostic of an acute exacerbation of activity within 10 and 14 days after the determination (Cases P. R. and T. M.).

The abnormal electrophoretic patterns were many and varied. In patients with long-standing or severe disease, the pattern remained abnormal when the disease was inactive clinically and when the C-reactive protein determination was negative (Cases E. K., M. J., J. C.). In one patient (Case R. R.), who was studied before mitral valvulotomy, embolic hemiplegia and not rheumatic activity may have been responsible for the abnormal electrophoretic pattern. The patient was clinically inactive preoperatively. The postoperative course was not characterized by recrudescence of rheumatic activity. Microscopic section of the left atrial appendix was normal.

COMMENT

Previous electrophoretic studies in rheumatic fever[1-5] have been on a small number of patients. They have stressed the occurrence of an increase in the alpha and gamma globulin components with an increase in the alpha globulin/albumin and gamma globulin/albumin ratios to more than twice normal. It has also been pointed out that this response is not specific for rheumatic fever. Dole and associates[3] reported six cases of scarlet fever, three of whom subsequently developed rheumatic fever. Both rheumatic and nonrheumatic patients showed depression of albumin, elevation of alpha-1 and alpha-2 globulins, and a delayed rise in gamma globulin. Furthermore, in a small series, Rutstein and associates[4] found the increase in globulins to persist when the disease was inactive.

Electrophoretic studies have been reported more recently in significantly larger numbers of patients by Malmros and Blix[5] and by Wilson and Lubschez,[6] and Lubschez.[12] These investigators confirm and extend the previous observations that electrophoretic abnormalities in rheumatic fever are not diagnostic. Lubschez[12] studied 30 normal children without antecedent disease and 27 normal children with antecedent disease. Changes in the postinfectious period similar to those in rheumatic fever were found in the albumin, alpha-1, alpha-2, and gamma globulin fractions. There were, however, no changes in the beta globulin fraction after infection in normal children. Furthermore, a beta globulin elevation was present in only one out of 42 patients with rheumatic fever.

In contradistinction, the beta globulin fraction was increased in seven out of thirty patients with rheumatic fever in our series. In two of these patients, this was the only abnormality. At first, it was thought that an increase in the beta globulin component might be peculiar to the rheumatic patient's immune re-

TABLE II

CASE	DIAGNOSIS	DURATION OF ILLNESS (DAYS)	TOTAL PROTEIN (GRAM %)	% TOTAL PROTEIN (AREA)					PROTEIN (GRAM %)						COMMENT
				ALBUMIN	GLOBULIN				ALBUMIN	GLOBULIN				A/G RATIO	
					ALPHA-1	ALPHA-2	BETA	GAMMA		ALPHA-1	ALPHA-2	BETA	GAMMA		
I. Normal Patterns															
Normals (Reiner et al.)	(80 cases)	Mean S.D.	7.23 0.54	56.0 2.8	7.2 1.3	8.8 1.9	13.1 2.5	14.7 2.6	4.30 0.33	0.50 0.11	0.60 0.17	0.90 0.27	1.00 0.21	1.29 0.16	
D. G., 12 yr., male, white	Acute pharyngitis; ? possible rheumatic fever	38	6.30	52.4	4.0	11.6	13.4	18.8	*3.30**	0.30	0.70	0.80	1.20	1.09	% alpha-2 and gamma slightly increased;† not diagnostic of rheumatic fever
R. S., 15 yr., female, white	Rheumatic fever, inactive	2½ yr. later	6.86	53.6	6.6	10.5	16.4	12.9	3.68	0.46	0.72	1.12	0.88	1.16	Corroborative of inactive state in presence of sedimentation rate of 20 mm./hr.
K. K., 15 yr., female, white	Chorea, mild	34 40	7.70 7.88	53.8 61.5	7.6 5.5	11.9 8.8	12.6 11.7	14.1 12.9	4.14 4.85	0.58 0.40	0.92 0.69	0.97 0.92	1.09 1.02	1.16 1.60	Alpha-2 slightly increased; corroboration of normal sedimentation rate
P. R., 10 yr., female, white	Recurrent acute rheumatic fever, mild; "cold"	41 46	7.05	52.2	6.7	12.1	15.8	13.2	3.68	0.47	0.85	1.11	0.93	1.09	Alpha-2 and beta slightly increased; not prognostic of activity 10 days later
F. M., 12 yr., male, white	Acute rheumatic fever, moderate, active (21 days after ACTH)	56	7.00	51.0	8.5	10.1	12.0	18.4	*3.57*	0.59	0.71	0.84	1.29	1.04	Gamma slightly increased; not indicative of activity which was present (fever, tachycardia)

J. O., 3½ yr., male, white	Acute rheumatic fever, mild, inactive; chicken pox (60 days after cortisone)	60	6.46	55.9	6.8	11.8	15.6	9.9	*3.61*	0.44	0.76	1.01	0.64	1.27	Gamma slightly decreased; % alpha-2 and beta slightly increased; corroborative of inactive state in presence of sedimentation rate of 27 mm.
E. W., 13 yr., female, white	Acute rheumatic fever; arthritis, chorea, mild, inactive	105	7.48	52.2	7.2	12.1	11.7	16.8	3.90	0.54	0.90	0.88	1.26	1.09	Alpha-2 slightly elevated; corroborative of inactive state
T. M., 13 yr., female, white	Acute recurrent rheumatic fever, mild, active (74 days after cortisone)	150	7.84	57.3	5.5	11.0	14.9	11.3	4.49	0.43	0.86	1.17	0.89	1.34	Alpha-2 slightly increased; not diagnostic of low-grade activity and not prognostic of obvious activity two weeks later
J. T., 11 yr., male, white	Chronic active rheumatic fever, mild	2 yr.	6.88	51.4	7.1	9.5	16.8	15.2	*3.53*	0.50	0.65	1.15	1.05	1.06	% beta slightly increased
II. Increased Alpha-2 Globulins															
J. T., 4 yr., male, white	Fever of unknown etiology; possible rheumatic fever	35	7.98	59.0	5.2	*12.2*	13.3	10.3	4.71	0.42	*0.97*	1.06	0.82	1.44	Total protein slightly increased
J. S., 7½ yr., male, white	Acute otitis media; rheumatic fever suspect	14 10 mo.	7.78 6.86	*48.5* 53.6	8.3 6.6	11.9 10.5	14.7 16.4	16.6 12.9	3.77 3.68	0.65 0.46	*0.93* 0.72	1.14 1.12	1.29 0.88	*0.94* 1.16	Total protein and % alpha-2 slightly increased; gram % alpha-1 and gamma increased because of high total protein
E. D. P., 6 yr., female, white	Possible rheumatic fever; tonsillitis	?	*8.33*	55.9	6.8	11.8	14.1	11.4	4.65	0.57	*0.98*	1.17	0.95	1.26	Gram % alpha-2 increased because of high total protein

*Numbers in italics indicate abnormal values.

†The slight increase or decrease of a component represents a variation from the normal mean by less than two standard deviations.

TABLE II (CONTINUED)

CASE	DIAGNOSIS	DURATION OF ILLNESS (DAYS)	TOTAL PROTEIN (GRAM %)	% TOTAL PROTEIN (AREA)					PROTEIN (GRAM %)						COMMENT
				ALBUMIN	GLOBULIN				ALBUMIN	GLOBULIN				A/G RATIO	
					ALPHA-1	ALPHA-2	BETA	GAMMA		ALPHA-1	ALPHA-2	BETA	GAMMA		
II.—Cont'd															
I. C., 10½ yr., male, white	Rheumatic fever, inactive; respiratory infection, severe	15	7.41	*44.9*	7.9	*17.1*	16.8	13.3	*3.33*	0.58	*1.26*	1.25	0.99	*0.82*	Slight increase in beta fraction; no increase in gamma globulin as result of infection in a rheumatic patient
G. M., 11 yr., male, white	Acute rheumatic fever, moderate	9	7.72	*39.2*	8.0	*16.2*	17.8	18.8	*3.02*	0.62	*1.25*	1.38	*1.45*	*0.65*	Beta and gamma moderately increased; early increase in all globulins chiefly alpha-2
S. G., 7½ yr., female, white	Acute rheumatic fever, moderate; respiratory infection	21 28	7.42	*43.0*	7.5	*16.7*	14.8	18.0	*3.19*	0.55	*1.24*	1.10	1.34	*0.75*	Gamma slightly increased
J. C., 15 yr., male, white	Rheumatic heart disease, inactive; severe congestive failure (3 wk. after cortisone)	60	*5.44*	*49.8*	7.1	*12.5*	15.7	14.8	*2.71*	0.39	0.68	0.86	0.81	0.99	% beta slightly increased
G. R.. 9 yr., male, white	Rheumatic heart disease, active, mild	46	7.30	54.6	6.2	*12.0*	14.0	13.2	3.99	0.45	0.88	1.03	0.95	1.20	Almost a normal pattern
P. T., 9 yr., female, white	Acute rheumatic fever, inactive	143	6.72	54.1	6.7	*13.4*	14.9	11.0	*3.64*	0.45	0.90	1.00	0.74	1.18	Gamma globulin slightly decreased

III. Increased Beta Globulins

B. F., 9 yr., male, white	Acute rheumatic fever, chorea, carditis, mild	21	6.94	*50.6*	7.6	8.1	*18.4*	16.4	*3.43*	0.53	0.56	1.28	1.14	0.98	% beta increased; gram % beta slightly increased
H. B., 12 yr., male, white	Chronic active rheumatic fever, mild	31 45	7.79 8.08	51.0 *49.8*	6.1 7.7	10.2 9.2	*18.7* *21.4*	14.0 11.9	3.97 4.03	0.48 0.62	0.79 0.74	*1.46* *1.73*	1.09 0.96	1.04 0.99	Slight fall in % gamma globulin

IV. Increased Gamma Globulins

J. W., 12 yr., male, Negro	Possible rheumatic fever	48	7.60	*49.6*	7.1	11.1	13.4	18.8	3.77	0.54	0.84	1.02	*1.43*	0.98	% alpha-2 and gamma globulin slightly increased; not diagnostic of rheumatic fever
J. P., 10½ yr., male, white	Possible rheumatic fever; mumps, moderate	97	7.02	*45.9*	6.4	12.0	14.3	*21.4*	*3.22*	0.45	0.84	1.00	*1.50*	*0.85*	Alpha-2 slightly increased; not diagnostic of rheumatic fever
S. S., 14½ yr., male, white	Acute recurrent rheumatic fever, moderate	17	7.76	*40.9*	6.7	10.6	14.0	*27.8*	*3.18*	0.52	0.82	1.08	*2.16*	*0.69*	Gram % alpha-2 slightly increased

V. Increased Alpha-1, Alpha-2 Globulins

G. R., 9 yr., male, white	Acute recurrent rheumatic fever, severe; pharyngitis	4 30	6.58	*36.4*	*13.3*	*20.3*	15.9	14.2	*2.39*	*0.88*	*1.33*	1.05	0.93	*0.57*	% beta increased slightly; no increase in gamma globulin with severe rheumatic fever
T. M., 13 yr., female, white	Acute recurrent rheumatic fever, mild	5 mo.	7.30	*50.3*	*9.4*	*12.5*	16.0	11.7	3.65	0.69	0.91	1.17	0.86	1.01	Slight increase of % beta; % gamma slightly decreased; slight increase of all globulins, except beta, in gram %

TABLE II (CONTINUED)

CASE	DIAGNOSIS	DURATION OF ILLNESS (DAYS)	TOTAL PROTEIN (GRAM %)	% TOTAL PROTEIN (AREA)					PROTEIN (GRAM %)						COMMENT
				ALBUMIN	GLOBULIN				ALBUMIN	GLOBULIN				A/G RATIO	
					ALPHA-1	ALPHA-2	BETA	GAMMA		ALPHA-1	ALPHA-2	BETA	GAMMA		
VI. Increased Alpha-1 and Gamma Globulins															
M. T., 15 yr., male, Negro	Acute rheumatic fever; respiratory infection, moderate	30	7.62	*37.9*	*10.0*	11.9	17.2	*23.0*	*2.89*	*0.76*	0.91	1.31	*1.75*	*0.61*	Slight increase of alpha-2 and beta
VII. Increased Alpha-2 and Beta Globulins															
M. J., 10 yr., male, white	Acute recurrent and chronic active rheumatic fever, severe and lengthy	4 days 1 yr., 6 mo.	6.52 *6.14*	*47.9* 49.3	6.0 7.1	*16.0* *14.0*	*18.8* *19.0*	11.3 10.6	*3.12* *3.03*	0.39 0.44	*1.04* 0.86	1.23 1.07	0.74 0.65	*0.92* *0.97*	Gram % beta slightly increased; gamma slightly decreased; slight increase alpha-2; low total protein; after 6 months of activity, no rise in gamma globulin; pattern persistently abnormal when inactive (C-protein neg.)
VIII. Increased Alpha-2 and Gamma Globulins															
P. G., 6 yr., female, white	Acute rheumatic fever, moderate	9	7.32	*37.5*	8.7	*13.5*	13.9	*26.4*	*2.76*	0.64	*1.00*	1.02	*1.94*	*0.61*	Alpha-2 slightly increased
M. M., 11 yr., female, white	Acute rheumatic fever, moderate; pharyngitis	14 28	8.00	*43.8*	7.7	*13.0*	14.0	*21.5*	*3.50*	0.62	*1.04*	1.12	*1.72*	*0.78*	Gram % alpha-1 slightly increased
IX. Increased Alpha-2, Beta, and Gamma Globulins															

IX. Increased Alpha-2, Beta, and Gamma Globulins															
E. K., 13 yr., male, white	Acute recurrent rheumatic fever; rheumatic heart disease, inactive (3 wk. after cortisone)	43	6.60	*38.9*	6.3	*12.8*	*19.3*	*23.2*	*2.5*	0.41	0.81	1.28	*1.53*	*0.64*	Gram % alpha-2 and beta globulins slightly increased; marked abnormalities despite inactive state (C-protein neg.)
X. Increased Beta and Gamma Globulins															
J. M., 11 yr., male, white	Acute rheumatic fever, moderate	43	7.90	*43.7*	4.0	11.3	*19.9*	*21.1*	*3.45*	0.32	0.89	*1.57*	*1.67*	*0.78*	Alpha-2 slightly increased
R. R., 37 yr., female, white	Cerebrovascular accident; rheumatic heart disease, inactive, preoperative commissurotomy	120	7.70	*43.8*	5.3	10.2	*19.0*	*21.7*	*3.37*	0.41	0.79	*1.46*	*1.67*	*0.78*	Abnormal pattern probably related to cerebrovascular accident
XI. Increased Alpha-1, Alpha-2, and Gamma Globulins															
C. A. J., 6½ yr., female, white	Acute rheumatic fever, very severe; respiratory infection	5	6.76	*33.8*	*12.7*	*17.2*	15.1	*21.3*	*2.29*	*0.86*	*1.15*	1.02	*1.44*	*0.51*	Death in 36 hours
G. C., 10 yr., female, white	Acute rheumatic fever, severe; tonsillitis	17 33	7.76	*28.7*	*12.6*	*15.9*	17.2	*25.6*	*2.23*	*0.98*	*1.23*	1.34	*1.98*	*0.40*	Beta increased slightly
XII. Increased Alpha-1, Alpha-2, Beta, and Gamma Globulins															
A. R., 13 yr., male, white	Acute recurrent rheumatic fever, severe	47	7.18	*29.6*	*13.5*	*16.4*	*20.7*	*19.8*	*2.13*	*0.97*	*1.18*	*1.49*	*1.42*	*0.74*	
A. B., 11½ yr., female, white	Acute rheumatic fever, severe	? 5 mo.	7.42	*24.4*	*13.7*	*18.8*	*19.1*	*24.0*	*1.81*	*1.02*	*1.39*	*1.42*	*1.78*	*0.32*	

sponse and might therefore be diagnostic. However, a careful study of the data of Wilson and Lubschez[6] revealed that the beta globulin fraction could be elevated within one week of a respiratory infection in a rheumatic patient who did not develop rheumatic fever but who subsequently showed an elevated gamma globulin. Similarly, an elevation of beta globulin was found in one of nine normal subjects with tonsillitis studied by Malmros and Blix.[5]

It is clear that the increase in the beta globulin fraction is not a specific response of the patient with rheumatic fever. However, there is a clear-cut difference in frequency of the beta abnormality in the rheumatic patient as compared to the nonrheumatic. Although not diagnostic, an elevated beta globulin fraction should strongly suggest rheumatic fever.

Our results agree with those of all previous investigators with regard to the elevation of the alpha-1, alpha-2, and gamma globulin components in rheumatic fever. Furthermore, there is nothing noteworthy about the gamma globulin response of the rheumatic fever patient in contrast to the normal patient with a respiratory infection. In fact, some patients in our series have shown no elevation of the gamma globulin fraction even after more than one month of rheumatic fever. The alpha-1 and alpha-2 globulin fractions may be elevated early or late in the disease and may persist despite the absence of rheumatic activity. An elevation in alpha-2 globulin was frequently associated with nonrheumatic inflammation.

From the foregoing discussion of our data and those in the literature, it is apparent that fractionation of the plasma proteins in rheumatic fever by electrophoresis provides no specificity to warrant its use as *the* diagnostic method. However, electrophoresis may confirm or strongly suggest the diagnosis of rheumatic fever in the presence of a high beta globulin fraction. Electrophoresis is of little absolute value in determining rheumatic activity. However, when normal and when used in conjunction with other laboratory tests, like the sedimentation rate and C-reactive protein determination, electrophoresis gives the clinician a greater security in deciding the termination of rheumatic activity.

SUMMARY

1. An analysis of 40 electrophoretic determinations of the serum proteins in thirty-six patients is the basis of this report.

2. It should be stressed that a beta globulin elevation was encountered in seven out of our thirty patients with rheumatic fever, whereas this fraction is rarely elevated in the postinfectious period of normal individuals (one out of thirty-six patients).

3. Although not specific, an elevated beta globulin fraction should strongly suggest the diagnosis of rheumatic fever.

4. Our data confirm the variability and nonspecificity of the other electrophoretic abnormalities in rheumatic fever. Changes in the alpha-1, alpha-2, and gamma globulins, alone and in combination, were observed.

5. A normal electrophoretic pattern may be obtained in the presence of rheumatic activity.

6. Electrophoretic abnormalities may persist when the disease is inactive clinically and when the C-reactive protein determination is negative.

7. Electrophoresis is of little *absolute* value in determining rheumatic activity. When used in conjunction with other laboratory tests, such as the sedimentation rate and C-reactive protein, a normal electrophoretic pattern gives the clinician a greater security in deciding the termination of rheumatic activity.

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STUDIES ON THE USE OF ETHAVERINE* IN THE TREATMENT OF ANGINA PECTORIS

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THE drug therapy of angina pectoris supposedly depends on substances producing coronary vasodilatation, thereby increasing the blood flow to ischemic myocardium. Many drugs with this supposed property have been suggested including papaverine,[1] visammin (Khellin),†[2,3] Peritrate,‡[4] and Paveril Phosphate.§[5]

European reports have been favorable on the use of ethaverine in angina pectoris.[6,7] A recent report in this country concluded the drug was of no more value in the treatment of angina pectoris than a placebo.[8] This report constitutes an additional evaluation of the effectiveness of ethaverine in the treatment of angina pectoris.

Ethaverine, the ethyl analogue of papaverine, differs from papaverine in that all the methonyl groups of the parent compound have been replaced with ethonyl groups. Chemically ethaverine is 6, 7-diethonyl-1-(3′, 4′-diethonyl benzyl)-isoquinaline. The peak coronary artery vasodilator effect and the length of time of maximum vasodilator effect of ethaverine and papaverine were compared in the isolated rabbit heart in 1950 by Winder and associates.[9] They found that ethaverine had both a more gradual and a more persistent action at doses above the threshold level than papaverine and that its total effect summed over time is more effective than papaverine.

Clinical reports are in agreement with its low toxicity relative to papaverine,[10-14] and Himmelsbach[15] reported that it is not habit forming.

METHODS AND MATERIALS

Twenty-two patients with well-established angina pectoris were chosen from the Cardiac Clinic Outpatient Dispensary of the Cincinnati General Hospital.

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Received for publication Feb. 26, 1954.

*Ethaverine is the generic name. The drug is known in Europe as Perparin and we are grateful to the National Drug Company, Philadelphia, Pa., for supplying us with this drug.

†Visammin is the generic name for dimethoxy-methyl-furano-chromone.

‡Brand name of pentaerythritol tetranitrate.

§Brand name of dioxyline phosphate.

The majority of these patients had been under observation in the clinic for many years for angina pectoris, and some were studied in previous investigations of the effects of drug therapy in angina pectoris in this laboratory.[3,5]

A double blind study was done at two dosage levels. The first and larger group received 50 mg. of ethaverine a day after meals and at bedtime, a total of 200 mg. The second and smaller group (patients taken from the first group) received 100 mg. of ethaverine after meals and at bedtime.

Daily records of the number of nitroglycerine tablets taken were recorded by the patient during each of three successive six-week periods. The first six weeks represented a control period, the second and third represented periods of therapy. However, the physicians (D. L. S. and A. I.) who dispensed the tablets during the last two periods did not know whether they were dispensing placebo or ethaverine, and the results tabulated at weekly intervals were not evaluated until both studies were completed. Following the control period patients were started on random choice of either drug or placebo. Placebo tablets identical in appearance and number with the drug were used.

One or more standard 12-lead electrocardiograms were taken on each patient during the control period, and one or two exercise-tolerance tests were carried out during the three periods on different days. The patients walked over two steps with an ice cube in each hand until angina or dyspnea developed.[16-18] If no end point was reached the test was terminated after the patient had performed the recommended number of trips for his age and weight as described by Master.[19,20] An electrocardiogram, including standard leads, unipolar extremity leads, and percordial leads V_4 and V_5 was taken prior to and immediately after completion of the exercise.

The results of the first group were tabulated and submitted to statistical analysis.

RESULTS

The patient's age, color, sex, diagnosis, and medication other than nitroglycerine, and number of nitroglycerine tablets used during the control, placebo, and drug periods in the first and larger group are found in Table I; the t and s values for this group are shown in Table II. It is evident that in comparing statistically the number of nitroglycerine tablets per week during placebo and drug periods of the first group, there is no statistical difference as the t value is 64 and the P is ($<0.6, >0.5$). Although not quite statistically significant ($t = 1.65$, $P = <0.1, >0.05$) there is a greater difference between the control period and drug period, than between the control period and placebo period ($t = 1.05$, $P = 0.3$). Although not statistically significant, we believe the improvement between the control period and both the placebo and drug periods may be partially explained on the psychic basis previously discussed by Brown and Riseman,[21] which has been generally known. The fact that the group shows a greater average improvement on drugs than on placebo would seem to indicate perhaps the drug has some favorable effect which is not statistically significant in our group.

TABLE I

NAME	AGE	COLOR	SEX	DIAGNOSIS	OTHER MEDICATION	NITROGLYCERINE PER WEEK		
						CONTROL	PLACEBO	DRUG
1. M. A.	71	W	F	HCVD	Digitalis	0.94	0.93	0.37
2. P. A.	56	W	F	Syph. CVD	Digitalis Quinidine	16.81	16.16	19.32
3. W. B.	52	W	M	ASHD HCVD Old CVA	None	22.48	25.5	22.58
4. L. C.	60	C	F	HCVD ASHD	None	21.14	15.55	13.5
5. G. C.	59	C	F	RHD	Digitalis	4.76	1.09	.53
6. C. D.	77	C	F	Syph. CVD	Thiomerin Digitalis	3.29	6.08	6.48
7. J. D.	66	W	M	HCVD Old infarct	Phenobarb.	14.49	3.16	3.49
8. G. D.	69	W	M	H & ASHD	Aminophyllin Phenobarb.	17.23	21.33	23.83
9. E. G.	71	W	M	A & HCVD	Mercurial Digitalis	3.9	4.0	2.08
10. H. G.	68	W	M	Old infarct	None	17.4	11.8	7.18
11. B. H.	75	W	F	Old infarct AS-HCVD	Mercurial Digitalis	14.6	4.3	6.0
12. A. H.	56	C	F	ASHD	None	11.72	11.38	13.37
13. C. H.	52	W	M	Old infarct	Phenobarb.	14.4	23.36	11.2
14. B. M.	67	W	F	ASHD	Thiomerin	6.33	3.41	2.33
15. J. W.	55	C	M	Old infarct	Digitoxin Thiomerin	3.14	.81	1.12
16. M. W.	68	W	F	HCVD	Phenobarb.	22.5	22.67	9.1
17. A. W.	51	C	F	HCVD	None	8.94	5.9	1.0
18. T. T.	70	W	F	HCVD	None	13.5	.79	5.0
19. A. S.	56	W	M	Old infarct ASHD	None	55.3	25.0	22.1
20. V. S.	70	C	F	HCVD	None	3.2	1.9	1.4
21. W. S.	74	W	M	ASHD	Digitalis	10.3	9.2	12.1
22. M. O.	52	C	F	HCVD	Phenobarb.	14.1	15.18	10.33

TABLE II

STATISTICAL ANALYSIS	t	P	
Control vs. placebo	1.05	0.3	
Control vs. drug	1.65	<0.1	>0.05*
Drug vs. placebo	0.64	<0.6	>0.5

*<0.05 is significant.

Table III lists the patients in the second smaller group treated on double dosage, and gives the number of nitroglycerine tablets used per week on both placebo and drug. It is seen that of the five patients, four took fewer nitroglycerine tablets while on placebo when compared to the drug period. This group was not submitted to statistical analysis due to its small number. No untoward reactions occurred due to ethaverine in either group.

TABLE III

NAME	MEDICINE	NUMBER PER WEEK OF NITROGLYCERINE
T. T.	Placebo	0.75
	Ethaverine	1.82
W. S.	Placebo	8.19
	Ethaverine	8.23
C. O.	Placebo	5.47
	Ethaverine	4.88
J. D.	Placebo	2.0
	Ethaverine	2.13
L. C.	Placebo	7.35
	Ethaverine	10.23

ELECTROCARDIOGRAPHIC SUMMARY

In the first group twenty out of the twenty-two patients had positive exercise-tolerance tests. No changes occurred during either the placebo or the drug periods. All five patients constituting the second group on double dosage had positive exercise-tolerance tests during the control period and no changes in configuration of the electrocardiogram or the tolerance to pain from exercise occurred.

DISCUSSION

Since no statistically significant improvement occurred at the dosage levels of ethaverine used in this study, ethaverine is probably not a valuable drug for the treatment of angina pectoris; however, since the drug did show some effect when compared to placebo, perhaps statistically significant results would be obtained if higher dosages were used in a larger series of cases under a carefully controlled

double-blind study. The carefully controlled studies referred to earlier by Voyles and associates[8] were substantially confirmed.

CONCLUSION

1. Ethaverine produced no statistically significant reduction in nitroglycerine requirements in twenty-two patients with angina pectoris.

2. Fewer nitroglycerine tablets were taken in both the placebo and ethaverine periods as compared to the control period. This is attributed in part to psychic factors.

3. Fewer nitroglycerine tablets were used during treatment with ethaverine than with placebo.

4. Further studies with ethaverine at higher doses and in larger series of cases seem indicated.

The authors wish to thank Mrs. Thella Laughlin and Mrs. Jean Patterson for their technical assistance.

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Clinical Reports

THE ASSOCIATION OF THE WENCKEBACH PHENOMENON WITH AURICULAR FLUTTER

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AURICULAR flutter, although frequently accompanied by some degree of atrioventricular block, is very rarely associated with the Wenckebach phenomenon. The only recorded cases in which it was the sole manifestation of a conduction defect are those of Lewis[1] and Scherf and Schott.[2] The following case is therefore of interest.

CASE REPORT

T.D., a 53-year-old bank manager, who had suffered from attacks of paroxysmal tachycardia for over twenty years, was admitted to Cardiff Royal Infirmary on July 21, 1953, complaining of palpitations which had been present for one month. Examination showed a heart rate of 140 per minute with dropped beats; blood pressure, 135/90 mm. Hg; congestive cardiac failure; displacement of the apex beat to the left; and an apical systolic murmur conducted to the axilla. Screening revealed uniform cardiac enlargement.

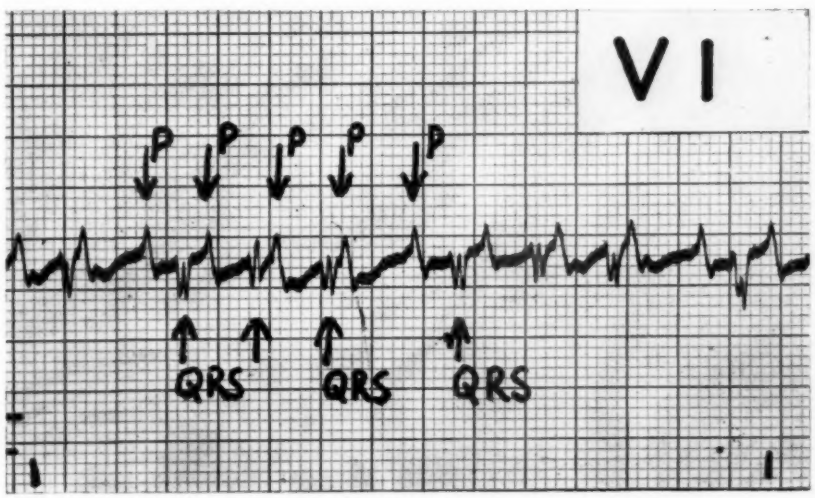

Fig. 1.

The electrocardiogram taken on the day of admission shows progressive lengthening of the P-R interval with failure of the ventricle to respond to every fourth beat (Fig. 1). There was no change with carotid sinus pressure. Two days later, following administration of Digoxin, there

From the Cardiac Dept., Royal Infirmary, Cardiff, Wales.
Received for publication Feb. 2, 1954.

was 2:1 block. The patient was then given quinidine 5 grains three times a day, and no conduction defect was apparent six days later when sinus rhythm had been restored. He was discharged on Aug. 2, 1953, on quinidine 5 grains twice a day but was readmitted on Aug. 30, 1953 with auricular flutter, the ventricular response being 1:1. Digitalis therapy was commenced and on Sept. 2, 1953, 30 grains quinidine were administered. The Wenckebach phenomenon reappeared on the following day to be succeeded on Sept. 4, 1953, by a higher and more irregular degree of heart block, which persisted until his discharge three weeks later.

On neither occasion was the diagnosis made clinically, and it is possible that the combination occurs not infrequently, but is overlooked.

I am indebted to Dr. William Phillips and to Professor Harold Scarborough for permission to publish details of this case.

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MITRAL AND TRICUSPID VALVOTOMY FOR MITRAL AND TRICUSPID STENOSIS

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THE autopsy studies of Cooke and White[1] and Smith and Levine[2] show that 10 to 20 per cent of patients with chronic rheumatic heart disease have tricuspid stenosis, but as the disability produced by this lesion is usually overshadowed by that caused by an associated mitral stenosis, there has been no attempt to treat tricuspid stenosis by valvotomy. The present patient who was suffering from rheumatic mitral and tricuspid stenosis has, however, had a mitral valvotomy and subsequently a tricuspid valvotomy.

CASE REPORT

The patient, a woman aged 22, developed breathlessness on exertion after chorea at the age of 15. In May, 1953, she sought advice as her disability was increasing, and she was breathless after climbing six stairs. She had never suffered from nocturnal dyspnea, hemoptysis, peripheral emboli, or congestive heart failure. For eight years she had a cough and green sputum in the winter but in the summer these symptoms cleared. She had been given digitalis by her practitioner.

On examination there was a malar flush but no cyanosis. The hands were cold. There was sinus rhythm but the peripheral pulse was of small volume. The blood pressure was 120/85 mm. Hg in the arms. Giant "a" waves were present in the jugular venous pulse (Fig. 1). The cardiac impulse indicated right ventricular hypertrophy. The second heart sound at the base was not palpable and there were no thrills. On auscultation at the apex there was a loud first heart sound, no systolic murmur, a second sound, and an opening snap followed by a diastolic murmur rising to a crescendo in presystole. The pulmonary second sound, although louder than the aortic second sound, was not very loud and not widely split. At the tricuspid area there was a diastolic murmur with a marked presystolic accentuation similar to the apical murmur. There was presystolic pulsation of the liver which was enlarged one finger's breadth below the costal margin.

The electrocardiogram showed tall pointed "P" waves in Lead II, an rSr pattern in Lead V_1, T-wave inversion in Leads III, V_1, V_2, and V_3 and biphasic negative, positive T waves in Leads V_4 and V_5 (Fig. 2).

On radiologic examination there were moderate generalized cardiac enlargement, normal pulmonary vessels, slight backward displacement of the esophagus by the left auricle, and enlargement of the right auricle and ventricle (Fig. 3).

From the clinical, electrocardiographic and radiologic signs mitral and tricuspid stenosis were diagnosed. The diagnosis of tricuspid stenosis was supported by the demonstration of an abnormal blood pressure gradient between right auricle and right ventricle at cardiac catheterization (Table I, Fig. 4).

From The City General Hospital and The Royal Hospital, Sheffield, England.
Received for publication Feb. 18, 1954.

Mitral valvotomy was performed on June 16, 1953. The fifth rib was resected through a left thoracotomy incision, and the mitral valve was approached through the left auricular appendix. There was a diaphragm stenosis with an orifice of 0.75 cm. diameter. The commissures split easily in both directions and subsequently the mobile cusps appeared to function normally and there was no regurgitation. The right auricle was inspected and was found to be abnormally distended through the cardiac cycle, but there was no evidence of tricuspid incompetence. The wall of the right auricle was invaginated, and an unsuccessful attempt made to palpate the tricuspid valve.

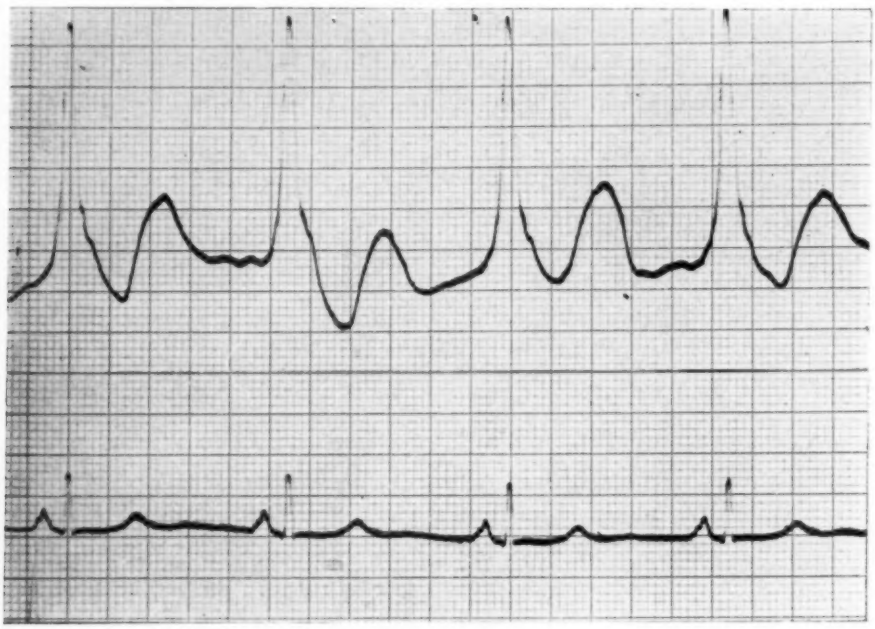

Fig. 1.—Synchronous records of the electrocardiogram and the jugular phlebogram showing giant "a" waves in a patient with tricuspid stenosis.

The postoperative course was uneventful and subsequently the patient noticed slight relief from the exertional dyspnea. There was little alteration in the physical signs. The sinus rhythm persisted. The blood pressure was 120/65 mm. Hg in the arms. The intensity of the first sound and the diastolic murmur diminished at the apex, and the diastolic murmur and its presystolic accentuation were then much better heard in the tricuspid area. Intracardiac blood pressures recorded by cardiac catheterization three weeks after operation showed that the abnormal gradient between right auricle and ventricle, which was considered evidence of tricuspid stenosis, persisted (Table I).

TABLE I. RESULTS OF CARDIAC CATHETERIZATION

	PULMONARY CAPILLARY BLOOD PRESSURE (mm. Hg)	PULMONARY ARTERY BLOOD PRESSURE (mm. Hg)	RIGHT VENTRICULAR BLOOD PRESSURE (mm. Hg)	RIGHT AURICULAR BLOOD PRESSURE (mm. Hg)	ARTERIO-VENOUS OXYGEN DIFFERENCE (ml./100 ml.)
Preoperative	6	23/15	25/5	20/10	4.5
After mitral valvotomy	5	18/10	18/7	19/12	6.4
After tricuspid valvotomy	5	23/13	23/3	17/7	5.4

In July, 1953, the patient was discharged from the hospital and apart from slight relief from her exertional dyspnea was little changed until October, 1953, when she developed attacks of palpitation which were sudden in onset and accompanied by intense dyspnea. An electrocardiogram recorded at this time showed auricular ectopic beats and although no electrocardiographic record was obtained during an attack of palpitation the patient was thought to be suffering from paroxysmal tachycardia and she was treated by quinidine, five grains twice daily. In spite of quinidine therapy she had occasional attacks and in November, 1953, she was admitted to the hospital as an emergency patient since she had lost consciousness during an attack.

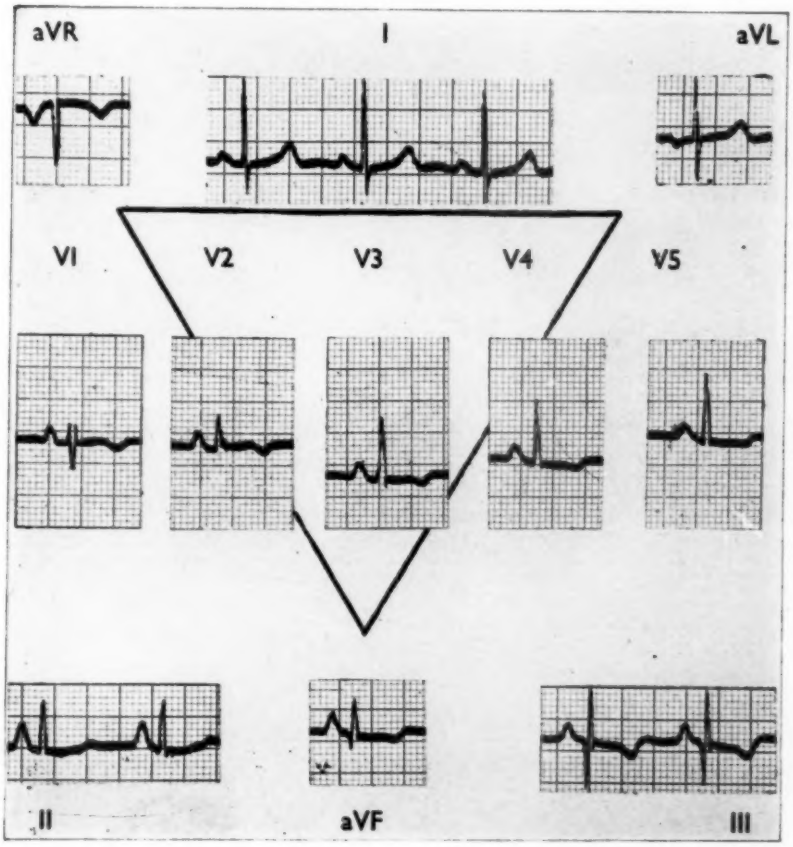

Fig. 2.—Electrocardiogram recorded before operation. The tall pointed "P" waves in Lead II are evidence of tricuspid stenosis.

Tricuspid valvotomy was performed on Nov. 17, 1953. The fifth rib was removed through a right thoracotomy incision and the tricuspid valve was approached through the right auricular appendix. The cusps of the valve were fused into a diaphragm and the orifice was 0.75 cm. in diameter. The medial and the posterior cusps were mobile but the anterior cusp was small and fibrous. There was slight regurgitation of blood into the auricle in ventricular systole. The commissures were split digitally until the orifice admitted two fingers. The regurgitant blood stream after the commissurotomy appeared no greater than that before.

Postoperatively the patient made an uninterrupted recovery and the subjective improvement was greater than after the mitral valvotomy. The most marked change in the physical signs was the diminution in the tricuspid diastolic murmur which became almost inaudible.

Blood pressure records obtained at cardiac catheterization a month after operation showed an abnormal gradient between right auricle and ventricle similar to that observed preoperatively (Table I). It was also noted that a positive wave had appeared in the auricular blood pressure record during ventricular systole, indicating slight tricuspid incompetence.

At review six weeks after discharge from the hospital, the patient said that she had become progressively less dyspneic and had experienced no further attacks of tachycardia. On examination the giant "a" waves had disappeared and there was only slight prominence of the auricular jugular venous wave.

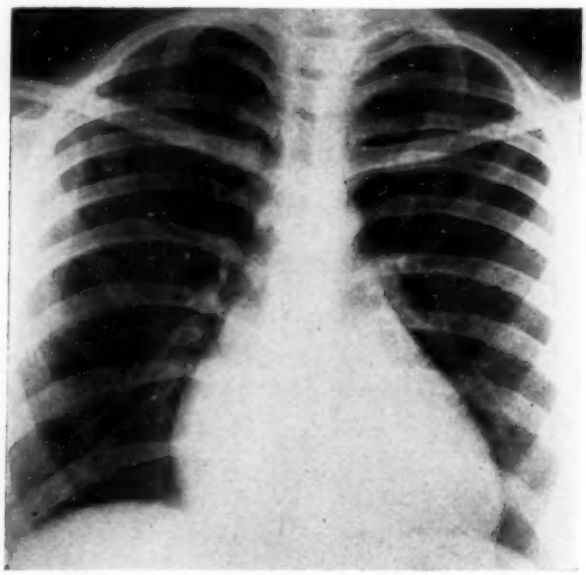

Fig. 3.—Posteroanterior teleradiogram showing generalized cardiac enlargement with increased prominence of the middle arc of the left cardiac border but normal pulmonary artery branches.

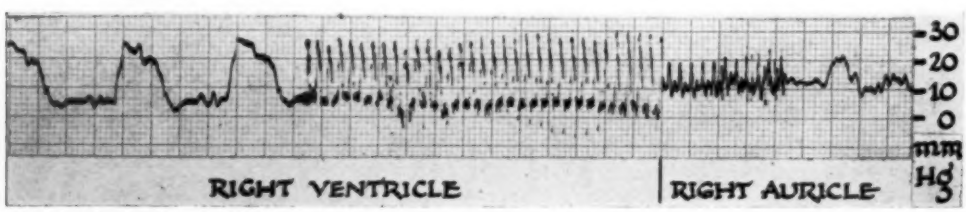

Fig. 4.—Blood pressure records from right ventricle and right auricle of a patient with tricuspid stenosis. The first portion of the record shows the right ventricular blood pressure curve with the record moving one large square in 0.2 sec. and the last portion shows the right auricular blood pressure curve at the same speed. The middle portion, recorded at one-tenth the speed, shows an abrupt change in blood pressure as the catheter was withdrawn from right ventricle to auricle. A detailed analysis is given in the text.

DISCUSSION

The diagnosis of tricuspid stenosis in the present patient was suggested by the giant "a" waves in the jugular venous pulse (Fig. 1), the presystolic hepatic pulsation, the loud rumbling diastolic murmur with presystolic accentuation in the tricuspid area, the tall peaked "P" waves in Lead II of the electrocardiogram

(Fig. 2) and right auricular enlargement on radiologic examination. Abnormally prominent "a" waves in the jugular venous pulse of patients with mitral stenosis are not necessarily a sign of associated tricuspid stenosis, since Whitaker[3] noted such waves in patients with only mitral stenosis who had severe complicating pulmonary hypertension. However, as there were no other clinical or radiologic signs of severe pulmonary hypertension in the present patient, the giant "a" waves suggested that there was tricuspid stenosis.

The blood pressures recorded at cardiac catheterization supported the clinical diagnosis. The absence of pulmonary hypertension was confirmed and an abnormal blood pressure gradient was found between right auricle and ventricle (Table I, Fig. 4). The auricular blood pressure was 5 mm. Hg higher than the ventricular blood pressure in diastole and 12 mm. Hg higher during auricular systole, when an abnormal auricular pulse pressure of 10 mm. Hg was recorded. These abnormal blood pressures in the right side of the heart were considered evidence of stenosis of the tricuspid valve. Similar abnormal blood pressures have been observed by Wood[4] who also found that patients with tricuspid stenosis had an abnormal pressure gradient from right auricle to ventricle even when they had auricular fibrillation. This abnormal pressure gradient across the tricuspid valve is an important sign of tricuspid stenosis since the most valuable clinical signs of the lesion disappear with the onset of auricular fibrillation.

In spite of the pulmonary capillary and pulmonary artery blood pressures being only slightly raised at rest, mitral valvotomy was considered a more desirable first operation than tricuspid valvotomy as the mitral stenosis appeared to be the most likely cause of the patient's dyspnea on exertion, and furthermore it seemed probable that relieving tricuspid stenosis would increase the output of the right ventricle and possibly precipitate acute pulmonary edema if mitral stenosis were present. The decision to perform a mitral valvotomy and observe its effect before operating on the tricuspid stenosis was supported by Brock's[5] experience. He found that patients with mitral and tricuspid stenosis were so relieved by mitral valvotomy that further treatment of the tricuspid lesion was unnecessary. In the present patient, however, tricuspid valvotomy was considered desirable after she had lost consciousness during an attack of tachycardia. The intracardiac blood pressure records, which showed a difference of 12 mm. Hg between right auricle and ventricle in auricular systole (Fig. 4) suggested that auricular systole played an important part in filling the right ventricle with blood, and the bout of unconsciousness was believed to be the result of an attack of paroxysmal tachycardia which made auricular systole ineffective and thus produced inadequate right ventricular filling and a fall in cardiac output. To prevent unconsciousness with subsequent attacks of tachycardia and to prepare the patient for the onset of auricular fibrillation, it was essential to relieve the tricuspid stenosis.

Although an abnormal blood pressure gradient persisted between right auricle and ventricle a month after tricuspid valvotomy (Table I), indicating that there was still some tricuspid stenosis, the subsequent regression of the giant "a" waves and the subjective improvement of the patient suggested that the operation had been beneficial.

SUMMARY

A patient with rheumatic mitral and tricuspid stenosis who was treated by mitral and tricuspid valvotomy is presented. An abnormal blood pressure gradient from right auricle to right ventricle is described as a sign of tricuspid stenosis.

We would like to thank Dr. James W. Brown for his constant advice on the management of the patient and Miss N. Hardy and Miss M. Aiken for technical assistance with the cardiac catheterization. We are also grateful to Dr. C. E. Davies and Prof. C. H. Stuart-Harris for permission to submit this report. The patient was at times under their care.

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IDIOPATHIC MYOCARDIAL HYPERTROPHY SIMULATING RHEUMATIC HEART DISEASE

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IDIOPATHIC hypertrophy of the heart is an unusual entity. Only twenty-four cases were collected by Levy and Von Glahn.[1] We observed a case of congenital idiopathic hypertrophy of the heart with clinical and radiographic findings compatible with rheumatic mitral valvular disease. The literature does not mention that such a similarity can occur.

CASE REPORT

E. K., a 25-year-old white male veteran entered this hospital Oct. 31, 1951, with the complaints of fever, productive cough, and pain in left chest. Past history revealed three previous admissions in the last 4 years. On each occasion the complaints consisted of fainting spells associated with palpitation, the seeing of yellow, the hearing of music, and unconsciousness. There were no tongue biting, convulsions, or incontinence. History of previous illnesses revealed childhood complaints questionably compatible with rheumatic fever. Physical examinations reported on each of these admissions showed a well-developed white male with a moderate funnel chest. Auscultation of the lungs revealed transitory wheezes, mainly inspiratory. The heart was enlarged to the left. A Grade 3 systolic murmur was heard best in the third intercostal space to the left of the sternum. The murmur was transmitted to the apex and to a lesser extent to the aortic area. No thrills were present and P_2 equaled A_2. The blood pressure varied from 98/68 to 114/66 mm. Hg. Rhythm was alternately regular and irregular.

A summation of the laboratory findings revealed a normal blood count, serology, glucose tolerance, and gastrointestinal series. The electroencephalogram revealed nonfocal bursts compatible with epilepsy. Electrocardiographic findings were: left ventricular hypertrophy, abnormal P waves, premature beats, and occasional bouts of auricular flutter with an auriculoventricular block varying from 2 to 1, to 4 to 1. The roentgenogram showed the heart to be 25 per cent above the predicted normal as measured on the height-weight tables. Cardiac fluoroscopy with barium swallow revealed definite left auricular and ventricular enlargement (Fig. 1, *A* and *B*).

On each admission prior to the last admission the patient was treated with quinidine and digitalis. He responded well with abatement of symptoms and conversion to normal sinus rhythm. Coughing or the drinking of cold water sometimes stopped the attacks. Pressure on the carotid sinus and eyeball did not aid.

On the final admission all the findings were similar except for fever, productive cough, and an increased sedimentation rate. He was treated with Gantrisin, quinidine, digitalis, and Dilantin. He rapidly became afebrile and asymptomatic and on the second day was ambulatory. On the evening of Nov. 14, 1951, the patient suddenly developed a slight cough with blood-streaked sputum; he gasped and expired.

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Received for publication March 3, 1954.

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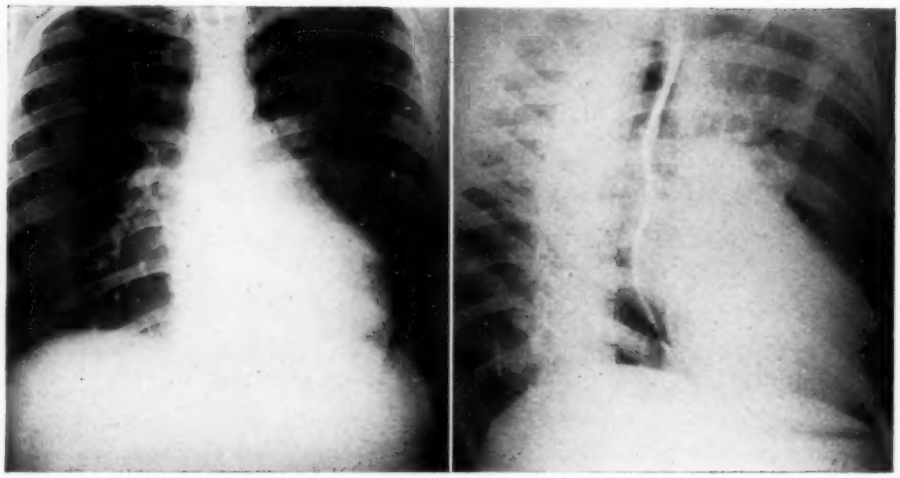

A. *B.*

Fig. 1.—*A*, Posteroanterior view of the chest. There is evidence of left ventricular enlargement, questionable enlargement of the left auricle to the right, and a small aortic knob shadow. *B*, Right anterior oblique view of the chest. Note enlargement of the left auricle.

Fig. 2.—Gross pathologic specimen of the heart showing mainly the left ventricle and auricle. The thickness of the ventricular wall is 30 mm.

Autopsy findings: Lungs showed a marked, frank pulmonary edema. Congestion of the liver, spleen, and kidneys was present. The heart weighed 750 grams and was markedly enlarged. The right ventricle was thickened and measured 5 mm. The left ventricle was also thickened and measured 30 mm. (Fig. 2). All valve measurements and the valve leaflets were normal. The left auricle appeared dilated and the auricular wall appeared somewhat hypertrophied, but there were no thrombi present. The left ventricular cavity revealed markedly thickened cordae tendineae. Papillary muscles and columna carnae were definitely hypertrophied. The endocardial surface appeared normal and no mural thrombi were present. The ostia of the coronary arteries were patent, and the right coronary artery was of normal size and had no atheromatous changes. The left coronary artery and its branches were somewhat smaller than usual. Cut section into the myocardium of right and left ventricle showed diffuse whitish, fibrotic streaking. There was no evidence of fresh infarction. The aorta revealed very little atheromatous change and seemed somewhat hypoplastic.

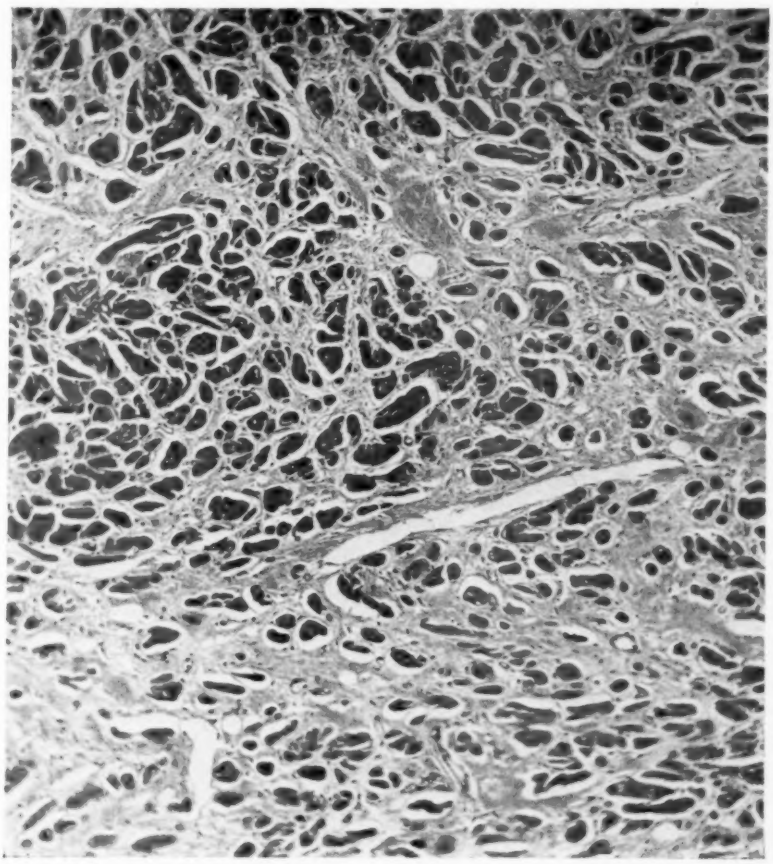

Fig. 3.—Microscopic view of the myocardium of the left ventricle (×60). Marked fibrosis is present.

Microscopic examination: Sections of the right ventricle and left ventricle showed diffuse fibrosis of interstitial areas with many hyperchromatic, blunted, and enlarged nuclei indicating myocardial hypertrophy (Fig. 3). Many of the muscle bundles were completely replaced with fibrous tissue and some show increase in acidophilic staining with loss of striation. The endocardium was not thickened. Careful examination of all sections failed to reveal any evidence of active or old rheumatic heart disease. The lungs showed marked alveolar edema.

SUMMARY

This 26-year-old white male patient was intermittently hospitalized for 1 to 2 years prior to death from congestive failure primarily because of cardiac arrhythmias. Autopsy findings revealed only massive cardiac hypertrophy primarily of the left ventricle with fibrosis of the myocardium and evidence of acute pulmonary edema with congestion of the liver, spleen, and kidneys. The etiology of the left ventricular and auricular hypertrophy and fibrosis was not apparent.

REFERENCE

1. Levy, R. L., and Von Glahn, W. C.: Cardiac Hypertrophy of Unknown Cause, A Study of the Clinical and Pathologic Features in Ten Adults, Am. Heart J. **28**:714, 1944.

Book Reviews

DAS ELEKTRISCHE HERZBILD. By Wilhelm Ernsthausen. (In Zusammenarbeit mit Dr. Franz Kienle.) 231 pages, 227 figures, München, 1953, Verlag für Biophysik Hermann Rinn.

The author presents in the book the theoretical basis of a new electrocardiographic procedure and its diagnostic application to various abnormal conditions. In five introductory chapters, the structural, chemical, and particularly the electrophysiological basis is discussed very competently (pp. 13 to 84). A great part of this treatment is highly mathematical (the author is an electrical engineer).

Of interest is quantitative information from experiments on dogs and sheep about the effect of the distance between heart and chest wall on the precordial ECG. The decrease of the amplitude with increasing distance is not identical for QRS and for T and is also different for various anatomic locations. The resulting distortion is due to various factors; the geometrical arrangement of electrical sources, the electrical conductivity of interlying tissues, area of electrodes and distance between electrodes, and different electrode resistance for the heart surface and chest wall.

The author concludes that spatial vector analysis from surface potentials is not justified without experimental proof that the distorting factors are relatively small (p. 84). It was not known to the author that such experimental proof has been recently provided for normal individuals (Schmitt, O., Levine, R., and Simonson, E.: AM. HEART J. 45:416, 1953) as well as for patients (Simonson, E., Schmitt, O., and Levine, R.: AM. HEART J. 45:655, 1953).

Since vector analysis was believed not to be applicable, the author proposes the following method: Numerous precordial bipolar electrocardiograms, 1.5 cm. apart, are taken with a fixed-electrode distance of 3.0 cm. The fluoroscopic heart shadow is outlined on the chest and framed in a rectangular coordinate system, exceeding the extreme right and left heart borders by 1 to 3 cm. Ten (horizontal hearts) to twelve (vertical hearts) horizontal lines are designated with letters and eight to fourteen vertical lines are numbered with 0 as the mid-line, positive to the left and negative to the right. The electrocardiograms are taken for all squares first with the bipolar electrode in horizontal position, and then with the electrode in vertical position. The resulting number of electrocardiograms varies between 190 and 240. The electrocardiograms are mounted on two sheets with the same coordinate system, one for the horizontal and the other one for the vertical "electrical heart picture."

It is, perhaps, somewhat surprising that the amplitudes are quite sizable, and in general comparable in magnitude to the standard leads, although smaller than the conventional chest leads. This system of bipolar chest leads is held to be superior to the V leads, because of the elimination of the central terminal, and a better local resolution. For analysis, a line is drawn connecting the equiphasic QRS complexes. This "phase-line" is comparable to the "null-line" in the analysis of spatial vectors in spite of the different interpretation.

Superimposing the horizontal and the vertical "electrical heart picture," the "phase-lines" intercept in one point from which the activation seems to radiate in two main directions: one to the left border, and the other one to the right border. The author finds that this pattern distribution resembles that on the heart surface of dogs, which is somewhat surprising in view of the distortion found in his own animal experiments. The center (intercept of the two phase-lines) is assumed to correspond to Schaefer and Trautwein's "Quellpunkt." Furthermore it is assumed that the potentials above and to the right of the phase-line reflect the electrical activity of the right ventricle, while those below and to the left of the phase-line project the electrical activity of the left ventricle (p. 105). This is a revival of Lewis' dextro- and levo-gram, and of Groedel's right and left partial ECG. In a way, it is also a revival of so-called "unipolar electrocardiography" (but without V leads), so far as the basic principle of interpretation of surface electrocardiograms as local patterns is concerned. This interpretation is not tenable since about 90 per cent of the potentials on any point of the body surface can be cancelled at anatomically roughly opposite points (AM. HEART J. 45:500, 1953).

From the pattern distribution in one of the horizontal coordinates the attempt is made to construct Lead I, and from one of the vertical coordinates Lead III by algebraic integration. In nine out of twelve experiments, the similarity is indeed, quite good. According to the author, this makes it possible to ". . . obtain information about the character of the elements of the limb ECG and to relate them to the function of single parts of the heart, such as right or left ventricle or anterior and posterior wall." However, the results are quite compatible with the interpretation on the basis of spatial vector analysis.

The author holds that the distribution of electrical patterns can be satisfactorily explained by the assumption of two imaginary groups of parallel fibers, arranged in the two directions of the spread of activation. With a time reference ECG, this apparent spread was measured in the two directions: the right ventricular excitation wave spreads from the cross section of the horizontal and vertical phase-line with a speed of 4 M./sec., and the left ventricular excitation wave spreads with a speed of 5.7 M./sec. These speeds are considerably higher than muscular conduction (1 M./sec.) and are identical with the conduction speed of Purkinje fibers.

From Fourier analysis to the twelfth harmonic, it was concluded that the heart may be considered as a fixed electrical source, with its spatial characteristics independent of amplitudes and phases of the ECG, and that QRS and T is a continuous process. These conclusions are at variance with other available information. The author did not make Fourier analyses for abnormal electrocardiograms.

The effect of the following fundamental types of pathology in the regional pattern distribution was investigated: local damage (including ischemia, infarct, bundle branch block), diffuse damage, ventricular hypertrophy, decompensation, and low voltage. In the last chapter, a graphic method of analysis is proposed as a "Functional Diagram of the Heart," essentially representing geometrical coordinates for the right and left ventricular ECG.

Important objections can be made against interpretation of surface electrocardiograms as local patterns. However, practical considerations are perhaps even more important for the critical appraisal of a new diagnostic method. Even if the theoretical basis is not valid or at least debatable, a new method might well, on an empirical basis, allow a better differentiation between normal and abnormal, or between the various abnormal conditions, than a conventional method. There is no doubt that the numerous precordial leads will give very detailed information about the pattern distribution on the anterior chest wall, and it is conceivable that this might be of diagnostic importance in certain conditions. However, no convincing proof of diagnostic superiority, supported by autopsy evidence, is given. Even if such a proof for certain conditions should still be forthcoming, the number of leads (up to 240) necessary to obtain the complete "electrical heart picture" is entirely impractical. For the construction of the "functional diagram of the heart" the author limits the leads to a wide horizontal band and vertical band of 3 to 4.5 cm. with a total of 44 leads, which is still too large for routine clinical use.

The "normal standard material" obtained in only 100 normal persons, without consideration of body build, age, and sex, is not adequate.

The book is somewhat cumbersome to read because of the use of numerous symbols and abbreviations, given in a list of 3½ pages in an appendix. Some of these symbols are, indeed, confusing; for instance, for the major QRS deflection, the author uses the symbol Sr or Sl, even if it is an R and not an S wave.

Although, at the present state, acceptance of this method for clinical electrocardiography cannot be expected, it has intriguing possibilities and deserves further exploration.

E. S.

EINFÜHRUNG IN DIE VEKTORIELLE DEUTUNG DES EKG. By Helmut Gillmann, M.D., 106 pages, Darmstadt, 1954, Dr. Dietrich Steinkopff Verlag, 83 figures.

In purpose and size this book is comparable to *Spatial Vector Electrocardiography*, by R. P. Grant and E. H. Estes, but it is more detailed in the discussion of the theoretical and experimental background. There is a brief but excellent historical introduction.

The view that the precordial leads are suitable for vector analysis is accepted and supported by experiments on the isolated animal hearts. In the analysis of vectors from precordial leads, a semiquantitative evaluation is made with an attempt to correct for proximity effects. This

correction is made from the distance between the various electrode positions and a hypothetical center (null point) on a diagram of the cross section of the chest, based on the average values of twenty-five normal persons. The QRS amplitude of V_2 is taken as 1.0, and the amplitudes of the other precordial leads are expressed in relative values of V_2.

The author shows in one normal case (p. 52) and in one abnormal case (p. 96) a good agreement between the actual and predicted amplitudes of the precordial leads "as a demonstration of the excellent agreement between theory and practice." Since the different precordial leads represent projections of different parts of the spatial loop, such agreement must appear fortuitous. This is an entirely empirical approach to arrive at a correction for the various electrode positions and has little to do with electrocardiographic theory, but it might be conceivably of practical merit. However, the only way to test an empirical correction is the evaluation of the error of prediction by statistical analysis with adequate material, and this was not done.

The author uses for analysis of spatial vectors not only the V leads, but also the CR, CL, and CF leads, because their axes are different. Any vector will coincide in the direction most closely with one or the other of these numerous leads, and this lead then will be the optimum for the projection of such vector. Therefore, this approach is called the "Optimalen schema" (scheme of optimals).

The use of such a large number of leads, however, in order to determine the direction of spatial vectors is far from optimum for two important reasons: (1) The direction of spatial vectors should be given in terms of azimuth and elevation rather than in terms of one of the conventional leads (including CR, CL, and CF), and (2) if one accepts the view (as the author does) that all leads are projections of a centrally located spatial vector, this vector can be calculated or constructed from the standard leads and the V leads without CR, CL, and CF leads.

In the application to abnormal conditions (pp. 66 to 98), however, the author makes little use of his "Optimalen schema." The essential information is obtained from Leads I to III and V_1 to V_6, although occasionally additional leads are taken. The spatial vectors are shown as projections on the frontal and horizontal plane as stereodiagrams, and this presentation is in certain respects superior to that of Grant and Estes.

One would not expect that an introduction is comprehensive, but since the greater part of the book is devoted to the fundamentals, it would have gained by consideration of the recent American literature. Two examples may serve as illustration. The author finds the variability of the augmentation ratio of the Goldberger leads too variable to be practical but ignores the more comprehensive study by Simonson and Keys (Circulation **1**:954, 1950). In regard to the mirror patterns of leads in anatomically opposite points the author refers to Swiss and French literature but does not refer to the larger and more precise quantitative information in the publications of Schmitt and associates. (Am. Heart J. **45**:416, 500, 655, 1954).

The book will serve its purpose as an introduction into spatial vector analysis, particularly for a reader who is interested in the theoretical basis as much as in the practical application.

E. S.

Announcements

A course in PRACTICAL ELECTROCARDIOLOGY will be presented during the week of December 6 to 10 under the auspices of University of Texas Postgraduate School of Medicine, Baylor University College of Medicine, and the Houston Heart Association. The guest lecturer, Dr. Demetrio Sodi-Pallares, Chief of the Department of Electrocardiology of the National Institute of Cardiology of Mexico City, will lecture each evening during the week from Monday through Friday from 7:30 P.M. to 10 P.M. During the daytime hours, registrants will be invited to attend the various hospitals in the Medical Center during periods when routine hospital tracings are being read by the hospital electrocardiologists. In addition, registrants in smaller groups will be given individualized instruction in interpretation of specific tracings by various members of the faculty of both schools who will be in attendance during the sessions.

The course, which includes adult and pediatric electrocardiology, is primarily designed to acquaint general practitioners as well as internists with practical aspects of electrocardiology, with emphasis upon those tracings commonly encountered in practice.

At a later date the details and schedule of the specific subjects to be discussed and the time and place of the various sessions will be announced.

The ANNUAL MEETING OF THE AMERICAN SOCIETY FOR THE STUDY OF ARTERIOSCLEROSIS will be held in the Sheraton Hotel, Chicago, Illinois, on October 31 and November 1, 1954.

Erratum

On page 268 of the August, 1954, issue in the article "Prolonged Depression of Atrioventricular Conduction Caused by Large Dosages of Protoveratrine" by Martin M. Black and Richard H. Lyons the nineteenth line from the top of the page should read ". . .500 μg protoveratrine tablets in place of 200 μg tablets previously used, resulting in an initial. . ."